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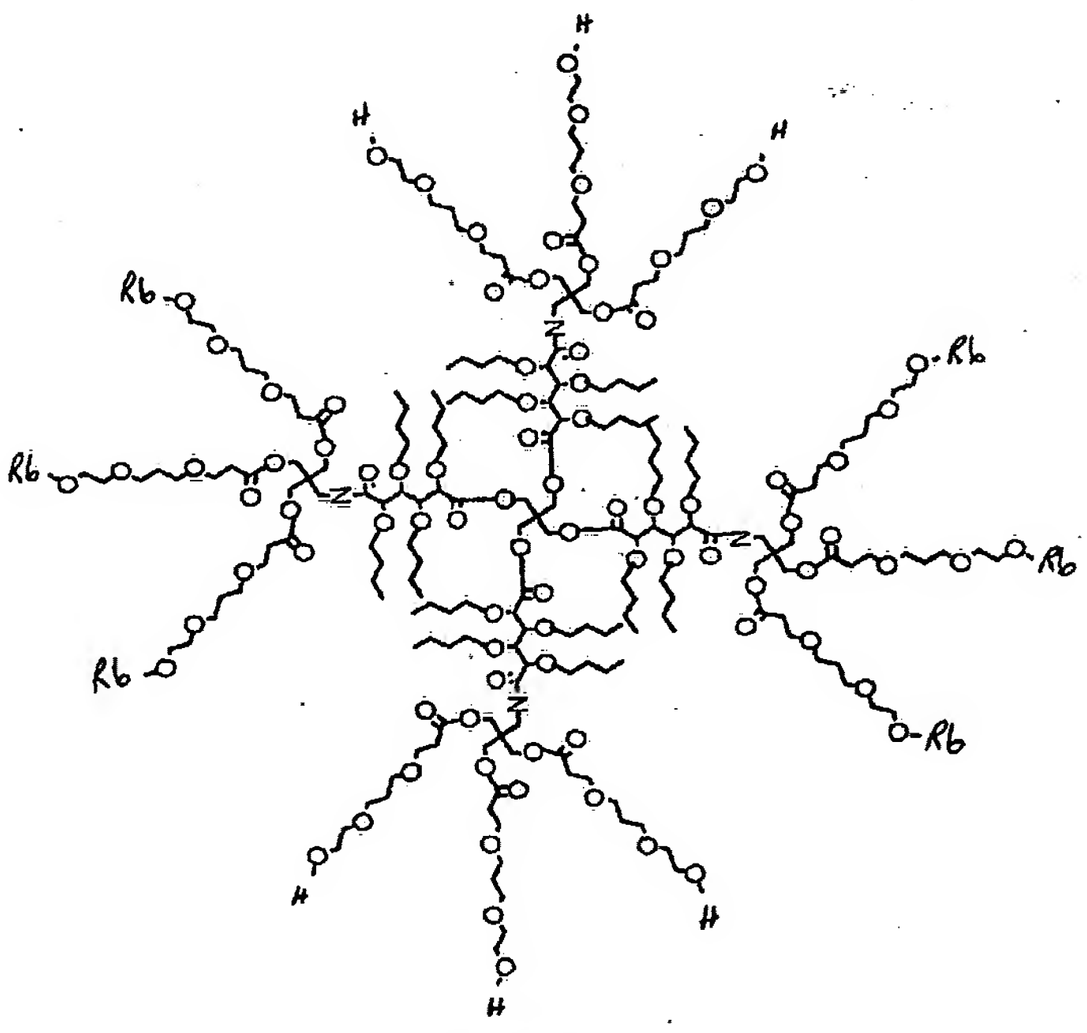
(54) Title: AMPHIPHILIC STAR-LIKE MACROMOLECULES FOR DRUG DELIVERY



(57) Abstract: The present invention provides polymeric compounds that can form micelles in solutions. These compounds have a hydrophobic, core that is coupled to a plurality of hydrophilic moieties.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Amphiphilic Star-Like Macromolecules for Drug Delivery

Priority of Invention

This application claims the benefit of the filing date of U.S. application Serial No. 60/304,965, filed July 12, 2001 and U.S. application Serial No. 60/333,310, filed November 23, 2001, under 35 U.S.C. § 119(e), the disclosures of which are incorporated by reference herein in their entirety

Government Funding

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Background of the Invention

Currently, there is a need for methods for delivering pharmaceutically active agents to patients in need of the active agent. One method for delivery is to encapsulate an active agent, such as, for example, a hydrophobic molecule in a polymer molecule wherein the polymer has a core that is coupled to a plurality of hydrophobic moieties.

Amphiphilic star-like macromolecules (ASMs) have been studied for drug delivery applications. (See, e.g., U.S. Patent Application Serial No. 09/298729 filed April 23, 1999; U.S. Patent Application Serial No. 09/422,295, filed October 21, 1999, and International Patent Application US00/10050 filed April 18, 2000.) The core-shell, amphiphilic structure of ASMs is covalently linked, which makes it thermodynamically stable as opposed to conventional micellar systems. Previously, aromatic cores were incorporated within the ASM structure but proved to be cytotoxic upon its degradation.

Polymeric micelles are a related type of amphiphilic block copolymers. These micelles have attracted attention as promising colloidal drug delivery systems (V. P. Torchilin J. Controlled. Release. **2001**, 73, 137; C. Allen, D. et al., Colloids and Surfaces B: Biointerfaces **1999**, 16, 3; and H. Otsuka, et al., Current Opinion in Colloid & Interface Science **2001,** 6, 3). In these colloidal systems, the hydrophobic block typically forms the core, essentially a "microcontainer" for a lipophilic pharmaceutical (K. Kataoka, et al., Adv. Drug Delivery Rev. **2001**, 47, 113). The hydrophilic part forms the outer shell, stabilizing the interface between the core and the external aqueous environment. Compared to traditional micellar systems, these polymeric surfactant-based drug carriers display apparent advantages such as lower critical micelle concentration (CMC), improved bioavailability, reduction of toxicity, enhanced permeability across the physiological barriers, and substantial changes in drug biodistribution.

Despite these advantages, the use of ASM's is somewhat limited, due to the difficulty in directing the release of the active agent at or near an appropriate target. Accordingly, there is a need for additional micellar systems and reverse micellar systems that possess some of the advantages associated with the thermodynamic stability of ASM's, but which can be used to direct active agents to specific targets.

Summary of the Invention

The present invention provides a compound having formula (I):

$$R^1\text{-}((R^2)_a\text{-}(R^3)_b\text{-}(R^4)_c\text{-}(R^5)_d\text{-}(R^6)_e)_n \qquad (I)$$

wherein:

a) R^1 is a core comprising a polyol or polyacid;

each R^2 independently is a divalent or polyvalent group having the formula $-X^1\text{-}R^8\text{-}(X^{1a})_g\text{-}$, wherein X^1 and X^{1a} are independently -C(=O)-, –

C(=S)-, –O–, –S–, -N(R^7)- or absent, and each R^8 is independently -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; a is 0 or an integer from 1 to about 10; and g is an integer from 1 to about 6;

each R^3 independently is a divalent dicarboxylic acid moiety having the formula -C(=O)-R^9-C(=O)-, wherein R^9 is an alkylene or cycloalkylene group containing from 1 to about 15 carbon atoms, substituted with a total of from 1 to about 10 hydroxy groups, wherein one or more of the hydroxy groups of the dicarboxylic acid are acylated with an acid residue; and b is an integer from 1 to about 10;

each R^4 independently is a divalent or polyvalent group having the formula –X^2-R^{10}-(X^{2a})$_h$-, wherein X^2 is -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; X^{2a} is -C(=O)-, -C(=S)-, –O–, –S–, or –N(R^7)– and R^{10} is -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; and c is 0 or an integer from 1 to about 10; and h is an integer from 1 to 6;

each R^5 independently is a group having the formula:

$$-R^{12}-(R^{11})_f-R^{12}-X^3-$$

wherein R^{11} is a sugar moiety; or a poly(alkylene oxide) or poly(alkylene imine) group having the formula -(–X^4–R^{13})-; wherein R^{13} is -(C_{2-40})alkylene- or branched -($C3_{-40}$)alkylene-; wherein each X^3 is independently -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; each X^4 is independently –O–, or –N(R^7)-; and f is an integer from about 2 to about 150; and d is from 1 to about 6;

each R^{12} is independently a bond, -(C_{1-40})alkylene- or branched -(C_{1-40})alkylene- groups, wherein each R^{12} is optionally substituted with one or more (e.g., 1, 2, or 3) functional groups. The functional groups are –OH, –OR^a, –NR^aR^b, -CO_2H, -SO_3H (sulfo), –CH_2–OH, –CH_2–OR^a, -CH_2-O-CH_2-R^a, and –CH_2–NR^aR^b; and X^4 is -O-, -S-, or –N(R^7)-;

wherein n is from 2 to 12; provided that a and b are not both zero; wherein each R^7 is independently selected from the group consisting of hydrogen, and $C_{(1-40)}$alkyl group, where the alkyl group can be a straight-chain or branched group; and R^a and R^b are each independently hydrogen (C_{1-8})alkyl, aryl, aryl(C_{1-8})alkylene; and

R^6 is hydrogen, are –OH, –OR^a, –NR^aR^b, -CO_2H, -SO_3H (sulfo), -CH_2-OH, –CH_2–OR^a, -CH_2-O-CH_2-R^a,–CH_2–NR^aR^b or a targeting moiety; provided that at least one R^6 group is a targeting moiety; and e is from 1 to about 6:

b) R^1 is a core comprising a polyol or polyacid;

each R^2 independently is a divalent or polyvalent group having the formula –X^1-R^8-$(X^{1a})_g$-, wherein X^1 and X^{1a} are independently -C(=O)-, –C(=S)-, –O–, –S–, -N(R^7)- or absent, and each R^8 is independently -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; a is an integer from 1 to about 10; and g is an integer from 1 to about 6;

each R^3 independently is a divalent dicarboxylic acid moiety having the formula -C(=O)-R^9-C(=O)-, wherein R^9 is an alkylene or cycloalkylene group containing from 1 to about 15 carbon atoms, substituted with a total of from 1 to about 10 hydroxy groups, wherein one or more of the hydroxy groups of the dicarboxylic acid are acylated with an acid residue; and b is an integer from 1 to about 10;

each R^4 independently is a divalent or polyvalent group having the formula –X^2-R^{10}-$(X^{2a})_h$-, wherein X^2 is -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; X^{2a} is -C(=O)-, -C(=S)-, –O–, –S–, or –N(R^7)– and R^{10} is -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; and c is 0 or an integer from 1 to about 10; and h is an integer from 1 to 6;

each R^5 independently is a group having the formula:

-R^{12}-$(R^{11})_f$-R^{12}-X^3-

wherein R^{11} is a sugar moiety; or a poly(alkylene oxide) or poly(alkylene imine) group having the formula -(–X^4–R^{13})-; wherein R^{13} is -(C_{2-40})alkylene- or branched -(C_{3-40})alkylene-; wherein each X^3 is independently -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; each X^4 is independently –O–, or –N(R^7)-; and f is an integer from about 2 to about 150; and d is from 1 to about 6;

each R^{12} is independently a bond, -(C_{1-40})alkylene- or branched -(C_{1-40})alkylene- groups, wherein each R^{12} is optionally substituted with one or more (e.g., 1, 2, or 3) functional groups. The functional groups are –OH, –OR^a, –NR^aR^b, -CO_2H, -SO_3H (sulfo), –CH_2–OH, –CH_2–OR^a, -CH_2-O-CH_2-R^a, and –CH_2–NR^aR^b; and X^4 is -O-, -S-, or –N(R^7)-;

wherein n is from 2 to 12; provided that a and b are not both zero; wherein each R^7 is independently selected from the group consisting of hydrogen, and $C_{(1-40)}$alkyl group, where the alkyl group can be a straight-chain or branched group; and R^a and R^b are each independently hydrogen (C_{1-8})alkyl, aryl, aryl(C_{1-8})alkylene; and

R^6 is hydrogen, are –OH, –OR^a, –NR^aR^b, -CO_2H, -SO_3H (sulfo), -CH_2-OH, –CH_2–OR^a, -CH_2-O-CH_2-R^a,–CH_2–NR^aR^b or a targeting moiety; and e is from 1 to about 6:

c) R^1 is a core comprising a polyol or polyacid;

each R^2 independently is a divalent or polyvalent group having the formula –X^1-R^8-(X^{1a})$_g$-, wherein X^1 and X^{1a} are independently -C(=O)-, –C(=S)-, –O–, –S–, -N(R^7)- or absent, and each R^8 is independently -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; a is 0 or an integer from 1 to about 10; and g is an integer from 1 to about 6;

each R^3 independently is a divalent dicarboxylic acid moiety having the formula -C(=O)-R^9-C(=O)-, wherein R^9 is an alkylene or cycloalkylene group containing from 1 to about 15 carbon atoms, substituted with a total of from 1 to

about 10 hydroxy groups, wherein one or more of the hydroxy groups of the dicarboxylic acid are acylated with an acid residue; and b is an integer from 1 to about 10;

each R^4 independently is a divalent or polyvalent group having the formula $–X^2\text{-}R^{10}\text{-}(X^{2a})_h\text{-}$, wherein X^2 is -C(=O)-, –C(=S)-, –O–, –S–, $–N(R^7)–$ or absent; X^{2a} is -C(=O)-, -C(=S)-, –O–, –S–, or $–N(R^7)–$ and R^{10} is $-(C_{1\text{-}8})$alkylene-, branched $-(C_{1\text{-}8})$alkylene- or $-(C_{6\text{-}10})$aryl-; and c is an integer from 1 to about 10; and h is an integer from 1 to 6;

each R^5 independently is a group having the formula:

$$-R^{12}\text{-}(R^{11})_f\text{-}R^{12}\text{-}X^3\text{-}$$

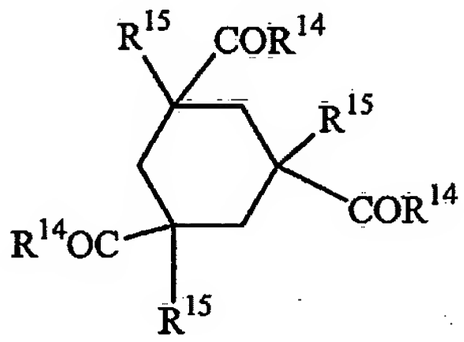
wherein R^{11} is a sugar moiety; or a poly(alkylene oxide) or poly(alkylene imine) group having the formula $-(–X^4–R^{13})\text{-}$; wherein R^{13} is $-(C_{2\text{-}40})$alkylene- or branched $-(C_{3\text{-}40})$alkylene-; wherein each X^3 is independently -C(=O)-, –C(=S)-, –O–, –S–, $–N(R^7)–$ or absent; each X^4 is independently –O–, or $–N(R^7)\text{-}$; and f is an integer from about 2 to about 150; and d is from 1 to about 6;

each R^{12} is independently a bond, $-(C_{1\text{-}40})$alkylene- or branched $-(C_{1\text{-}40})$alkylene- groups, wherein each R^{12} is optionally substituted with one or more (e.g., 1, 2, or 3) functional groups. The functional groups are –OH, $–OR^a$, $–NR^aR^b$, $-CO_2H$, $-SO_3H$ (sulfo), $–CH_2–OH$, $–CH_2–OR^a$, $-CH_2\text{-}O\text{-}CH_2\text{-}R^a$, and $–CH_2–NR^aR^b$; and X^4 is -O-, -S-, or $–N(R^7)\text{-}$;

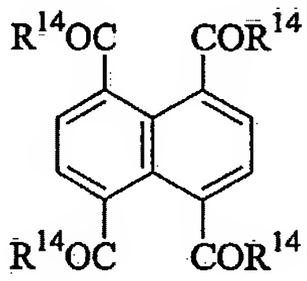
wherein n is from 2 to 12; provided that a and b are not both zero; wherein each R^7 is independently selected from the group consisting of hydrogen, and $C_{(1\text{-}40)}$alkyl group, where the alkyl group can be a straight-chain or branched group; and R^a and R^b are each independently hydrogen $(C_{1\text{-}8})$alkyl, aryl, aryl$(C_{1\text{-}8})$alkylene; and

R^6 is hydrogen, are –OH, –OR^a, –NR^aR^b, -CO_2H, -SO_3H (sulfo), -CH_2-OH, –CH_2–OR^a, -CH_2-O-CH_2-R^a,–CH_2–NR^aR^b or a targeting moiety; and e is from 1 to about 6:

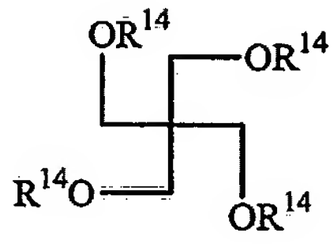
d) R^1 is a core comprising a polyacid moiety having the formula



or



or a pentaerythritol polyol having the formula



;

wherein each R^2 independently is a divalent or polyvalent group having the formula –X^1-R^8-(X^{1a})$_g$–, wherein X^1 and X^{1a} are independently -C(=O)-, –C(=S)-, –O–, –S–, =N(R^7)- or absent, and each R^8 is independently -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; a is 0 or an integer from 1 to about 10; and g is an integer from 1 to about 6;

each R^3 independently is a divalent dicarboxylic acid moiety having the formula -C(=O)-R^9-C(=O)-, wherein R^9 is an alkylene or cycloalkylene group containing from 1 to about 15 carbon atoms, substituted with a total of from 1 to about 10 hydroxy groups, wherein one or more of the hydroxy groups of the dicarboxylic acid are acylated with an acid residue; and b is an integer from 1 to about 10;

each R^4 independently is a divalent or polyvalent group having the formula $-X^2-R^{10}-(X^{2a})_h-$, wherein X^2 is -C(=O)-, –C(=S)-, –O–, –S–, $-N(R^7)-$ or absent; X^{2a} is -C(=O)-, -C(=S)-, –O–, –S–, or $-N(R^7)-$ and R^{10} is -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; and c is 0 or an integer from 1 to about 10; and h is an integer from 1 to 6;

each R^5 independently is a group having the formula:

$$-R^{12}-(R^{11})_f-R^{12}-X^3-$$

wherein R^{11} is a sugar moiety; or a poly(alkylene oxide) or poly(alkylene imine) group having the formula -(–X^4–R^{13})-; wherein R^{13} is -(C_{2-40})alkylene- or branched -(C_{3-40})alkylene-; wherein each X^3 is independently -C(=O)-, –C(=S)-, –O–, –S–, $-N(R^7)-$ or absent; each X^4 is independently –O–, or $-N(R^7)-$; and f is an integer from about 2 to about 150; and d is from 1 to about 6;

each R^{12} is independently a bond, -(C_{1-40})alkylene- or branched -(C_{1-40})alkylene- groups, wherein each R^{12} is optionally substituted with one or more (e.g., 1, 2, or 3) functional groups. The functional groups are –OH, $=OR^a$, $-NR^aR^b$, $=CO_2H$, $-SO_3H$ (sulfo), $=CH_2-OH$, $-CH_2-OR^a$, $-CH_2-O-CH_2-R^a$, and $-CH_2-NR^aR^b$; and X^4 is -O-, -S-, or $-N(R^7)-$;

wherein n is from 2 to 12; provided that a and b are not both zero; wherein each R^7 is independently selected from the group consisting of hydrogen, and $C_{(1-40)}$alkyl group, where the alkyl group can be a straight-chain or branched group; and R^a and R^b are each independently hydrogen (C_{1-8})alkyl, aryl, aryl(C_{1-8})alkylene; and

R^6 is hydrogen, are –OH, $-OR^a$, $-NR^aR^b$, $-NH_2$, $-CO_2H$, $-SO_3H$ (sulfo), $-CH_2-OH$, $-CH_2-OR^a$, $-CH_2-O-CH_2-R^a$, $-CH_2-NR^aR^b$ or a targeting moiety; and e is from 1 to about 6.

Additionally, compounds of formula (I) having unsaturated bonds (e.g., in the fatty acid or polyether groups), can be cross-linked to form covalently bonds in the hydrophobic portion.

Accordingly, the invention provides a compound of formula (I) as described above. Such compounds of formula (I) are useful intermediates for preparing micelles that can be used in drug delivery applications and that can be cross-linked to provide cross-linked macromolecules that are also useful in drug delivery applications.

The invention also provides an encapsulate comprising a molecule surrounded or partially surrounded by a macromolecule of the invention.

The invention also provides a method for preparing an encapsulate of the invention comprising combining compounds of formula (I) and a molecule (*e.g.*, a therapeutic agent) in a solvent, and allowing the compounds of formula (I) to aggregate around the molecule, to provide the encapsulate (*i.e.*, the molecule surrounded or partially surrounded by compounds of formula (I)).

The invention also provides a pharmaceutical composition comprising an encapsulate of the invention (*i.e.*, a therapeutic agent surrounded or partially surrounded by compounds of formula (I)); and a pharmaceutically acceptable carrier.

The invention also provides a pharmaceutical composition comprising an encapsulate of the invention (*i.e.*, a therapeutic agent encapsulated in a cross-linked macromolecule); and a pharmaceutically acceptable carrier.

The invention also provides a method for modulating the release of a therapeutic agent from a pharmaceutical composition comprising administering an encapsulate of the invention to an animal in need of treatment. The encapsulate can modulate the release of therapeutic agents by controlling the adsorption of the active agent encapsulated within the encapsulate through the skin of the animal.

The invention also provides a method for delivering a therapeutic agent to an animal in need of treatment with the agent comprising administering an encapsulate of the invention comprising the agent to the animal.

The invention also provides intermediates and processes useful for preparing compounds of formula (I) as described herein.

The invention also provides for the use of a compound of formula (I) to prepare a medicament useful for treating or preventing an illness or a disease.

The invention also provides a method for using a compound of formula (I) to (a) sequester lipoproteins from macromolecular depots such as proteoglycans that heighten atherogenic tendencies; (b) reduce lipoprotein oxidation (which leads to unregulated uptake of low-density lipoproteins (LDL) by macrophages, transforming them into foam cells, the precursors to atherosclerosis); and (c) enhance lipoprotein transport and clearance (via macrophages, and the liver). The compounds having formula (I) can be administered to a patient in need of reducing the concentration of lipoproteins and minimize cardiovascular diseases caused by the presence of excess LDL in the blood.

Brief Description of the Figures

Figures 1 and 2 illustrate representative reactions for attaching the targeting moiety, biotin, to a polyalkylene oxide (R^5) group.

Figure 3 illustrates a representative reaction for acylation of a divalent dicarboxylic acid moiety, (R^3 group).

Figure 4 illustrates a representative reaction for attaching R^3 groups to prepare a compound of the invention.

Figure 5 illustrates two compounds that can be incorporated in the compounds of the invention as targeting moieties.

Figure 6 illustrates a representative reaction for attaching a polyethylene oxide (R^5) group to prepare a compound of the invention.

Figure 7 illustrates a representative reaction for cross-linking the compounds of the invention having unsaturation in the R^5 groups to prepare a covalently stabilized compound of the invention.

Figures 8, 9, 10, and 11 illustrate representative compounds of the invention.

Detailed Description

As used herein the term "polyol" includes straight chain and branched chain aliphatic groups, as well as mono-cyclic and poly-cyclic aliphatics, which are substituted with two or more hydroxy groups. A polyol typically has from about 2 carbons to about 20 carbons; preferably, from about 3 carbons to about 12 carbons; and more preferably from about 4 carbons to about 10 carbons. A polyol also typically comprises from about 2 to about 20 hydroxy groups; preferably from about 2 to about 12 hydroxy groups; and more preferably from about 2 to about 10 hydroxy groups. A polyol can also optionally be substituted on a carbon atom with one or more (e.g., 1, 2, or 3) carboxy groups (COOH). These carboxy groups can conveniently be used to link the polyol to the polyether in a compound of formula (I).

Polyols that are suitable for use as the polymer core are nearly limitless. Aliphatic polyols having from 1 to 10 carbon atoms and from 1 to 10 hydroxyl groups may be used, including ethylene glycol, alkane diols, alkyl glycols, alkylidene alkyl diols, alkyl cycloalkane diols, 1,5-decalindiol, 4,8-bis(hydroxymethyl)tricyclodecane, cycloalkylidene diols, dihydroxyalkanes, trihydroxyalkanes, and the like. Cycloaliphatic polyols may also be employed, including straight chained or closed-ring sugars and sugar alcohols, such as mannitol, sorbitol, inositol, xylitol, quebrachitol, threitol, arabitol, erythritol,

adonitol, dulcitol, fucose, ribose, arabinose, xylose, lyxose, rhanmose, galactose, glucose, fructose, sorbose, mannose, pyranose, altrose, talose, tagitose, pyranosides, sucrose, lactose, maltose, and the like. Additional examples of aliphatic polyols include derivatives of glyceraldehyde, glucose, ribose, mannose, galactose, and related stereoisomers.

Other R^1 polyols that may be used include cyclic crown ethers, cyclodextrines, dextrines and other carbohydrates such as starches and amylose. Alkyl groups may be straight-chained or branched, and may contain from 1 to 10 carbon atoms.

The term "polyacids" as used herein include compounds which have two or more acid groups per molecule. Preferably, the polyacid is a dibasic, tribasic or polybasic carboxylic acid functional compound. The polyacid can generally be aliphatic, cycloaliphatic or aromatic. Examples of polyacids include compound such as cyclodextrans and calerixane.

Specific R^3 groups are formed from di-carboxylic acids containing from 1 to about 10 carbon atoms and substituted with from 1 to about 10 hydroxyl groups. The mono-or di-carboxylic acid may be a straight chained or branched chained aliphatic, or a mono-cyclic or poly-cyclic aliphatic compound. Suitable dicarboxylic acids include mucic acid, malic acid, citromalic acid, alkylmalic acid, hydroxy derivatives of glutacic acid, and alkyl glutadc acids, tartadc acid, citric acid, hydroxy derivatives of rumadc acid, and the like. Suitable monocarboxylic acids include 2,2-(bis(hydroxymethyl)propionic acid, and N-[*tris*(hydroxymethyl)methyl]glycine (tricine).

Specific "sugar moieties" include monosaccharides, disaccharides, trisaccharides, and polysaccharides. Non-limiting examples of sugar moieties include straight chained or closed-ring sugars and sugar alcohols, such as, for example, mannitol, sorbitol, inositol, xylitol, quebrachitol, threitol, arabitol, erythritol, adonitol, dulcitol, fucose, ribose, arabinose, xylose, lyxose, rhanmose,

galactose, glucose, fructose, sorbose, mannose, pyranose, altrose, talose, tagitose, pyranosides, sucrose, lactose, maltose, and the like. Additional examples of aliphatic polyols include derivatives of glyceraldehyde, glucose, ribose, mannose, galactose, and related stereoisomers. Preferred sugar moieties are glucose, sucrose, fructose, ribose, and the like, and deoxy sugars such as deoxyribose, and the like. Saccharide derivatives can conveniently be prepared by methods known to the art. Examples of suitable mono-saccharides are xylose, arabinose, ribose, and the like. Examples of di-saccharides are maltose, lactose, sucrose, and the like. Examples of suitable sugar-alcohols are erythritol, sorbitol, and the like.

As used herein, the term polyether includes poly(alkylene oxides) having between about 2 and about 150 repeating units. Typically, the poly(alkylene oxides) have between about 50 and about 110 repeating units. The alkylene oxide units contain from 2 to 10 carbon atoms and may be straight chained or branched. Preferably, the alkylene oxide units contain from 2 to 10 carbon atoms. Poly(ethylene glycol) (PEG) is preferred. Alkoxy-, amino-, carboxy-, and sulfo-terminated poly(alkylene oxides) are preferred.

In a compound of formula (I), a poly(alkylene oxide) can be linked to a polyol, for example, through an ether, thioether, amine, ester, thioester, thioamide, or amide linkage. Preferably, a poly(alkylene oxide) is linked to R^3 by an ester or amide linkage in a compound of formula (I).

As used herein, the term polyimine includes poly(alkylene imines) having between about 2 and about 150 repeating units. Typically, the poly(alkylene imines) have between about 50 and about 110 repeating units. The alkylene imine units contain from 2 to 10 carbon atoms and may be straight chained or branched. Preferably, the alkylene imine units contain from 2 to 10 carbon atoms. Poly(ethylene imine) (PEI) is preferred. Alkoxy-, amino-, carboxy-, and sulfo-terminated poly(alkylene imines) are preferred.

In a compound of formula (I), a poly(alkylene imine) can be linked to a polyol, for example, through an ether, thioether, amine, ester, thioester, thioamide, or amide linkage. Preferably, a poly(alkylene imine) is linked to R^3 by an ester or amide linkage in a compound of formula (I).

As used herein, the term "targeting moiety" refers to groups that have an ability to direct the encapsulated active agents to a site where the activity from the active agent is desired. In the present invention the polymers can have one or more targeting moiety. Non-limiting examples of targeting moieties include but are not limited to groups such as, for example, $-CO_2H$, $-SO_3H$ (sulfo), $-NH_2$, or groups derived from compounds such as, for example, biotin, streptavidin, sugar moieties, folic acid, amino acids and peptides.

As used herein, the term fatty acid includes fatty acids and fatty oils as conventionally defined, for example, long-chain aliphatic acids that are found in natural fats and oils. Fatty acids typically comprise from about 2 to about 24 carbon atoms. Preferably, fatty acids comprise from about 6 to about 18 carbon atoms. The term "fatty acid" encompasses compounds possessing a straight or branched aliphatic chain and an acid group, such as a carboxylate, sulfonate, phosphate, phosphonate, and the like. The "fatty acid" compounds are capable of "esterifying" or forming a similar chemical linkage with hydroxy groups on the polyol. Examples of suitable fatty acids include caprylic, capric, lauric, myristic, myristoleic, palmitic, palmitoleic, stearic, oleic, linoleic, eleostearic, arachidic, behenic, erucic, and like acids. Fatty acids can be derived from suitable naturally occurring or synthetic fatty acids or oils, can be saturated or unsaturated, and can optionally include positional or geometric isomers. Many fatty acids or oils are commercially available or can be readily prepared or isolated using procedures known to those skilled in the art.

As used herein the term "amino acid," comprises the residues of the natural amino acids (e.g. Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Hyl, Hyp, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val) in D or L form, as well

as unnatural amino acids (e.g. phosphoserine, phosphothreonine, phosphotyrosine, hydroxyproline, gamma-carboxyglutamate; hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4,-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, citruline, a-methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, and tert-butylglycine). The term also comprises natural and unnatural amino acids bearing a conventional amino protecting group (e.g. acetyl or benzyloxycarbonyl), as well as natural and unnatural amino acids protected at the carboxy terminus (*e.g.*, as a $(C_1\text{-}C_6)$alkyl, phenyl or benzyl ester or amide; or as an *- methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art (See for example, T.W. Greene, *Protecting Groups In Organic Synthesis*; Wiley: New York, 1981, and references cited therein). An amino acid can be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus, or through any other convenient point of attachment, such as, for example, through the sulfur of cysteine.

As used herein, the term "peptide" describes a sequence of 2 to 25 amino acids (*e.g.*, as defined hereinabove) or peptidyl residues. The sequence may be linear or cyclic. For example, a cyclic peptide can be prepared or may result from the formation of disulfide bridges between two cysteine residues in a sequence. A peptide can be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus, or through any other convenient point of attachment, such as, for example, through the sulfur of a cysteine. Preferably a peptide comprises 3 to 25, or 5 to 21 amino acids. Peptide derivatives can be prepared as disclosed in U.S. Patent Numbers 4,612,302; 4,853,371; and 4,684,620. Peptide sequences specifically recited herein are written with the amino terminus on the left and the carboxy terminus on the right.

It is understood that in the compounds of the invention where R^2 is a polyvalent moiety one valence is attached to R^1 and each of the other valences is attached to a group having the formula $-(R^3)_b-(R^4)_c-(R^5)_d-(R^6)_e$ where each R^3, R^4, R^5, R^6, b, c, d, and e independently have the meanings described herein above.

It is understood that in the compounds of the invention where R^4 is a polyvalent moiety one valence is attached to R^3 and each of the other valences is attached to a group having the formula $-(R^5)_d-(R^6)_e$ where each R^5, R^6, d, and e independently have the meanings described herein above.

As used herein, a "cross-linked macromolecule" means a micelle that has been cross-linked to provide a covalently cross-linked structure.

As used herein, the term "encapsulate" means a composition, having a molecule (*e.g.*, a therapeutic agent) surrounded or partially surrounded by at least one compound of formula (I). The term encapsulate includes structures wherein the compound of formula (I) has been cross-linked, as well as structures wherein the compound of formula (I) has not been cross-linked.

The compounds of formula (I) that comprise unsaturated bonds can be cross-linked to form more stabilized polymers, which comprise a compound of formula (I) that have been covalently linked.

Typically, the polymers of the invention have a diameter of from about 10 nm to about 1000 nm. The diameters can be measured using any suitable analytical technique, such as, for example, dynamic light scattering.

Compounds of formula (I) can be used for drug solubilization, fragrance encapsulation, passive and active targeting for drug delivery, waste water treatment, enhanced capillary electrophoresis activation, and induction of protein crystallization.

Accordingly, as used herein, the term "molecule" includes any compound that can be incorporated into a polymer or a cross-linked polymer as

described herein. Typically, "molecules" have solubility properties that are undesirable and that can be modified by incorporation into an amphiphilic polymer or a cross-linked polymer of the invention. For example, the term "molecule" includes therapeutic agents, insecticides, pesticides, herbicides, antiseptics, food additives, fragrances, dyes, diagnostic aids, and the like. Other specific examples of molecules include, but are not limited to:

abietic acid, aceglatone, acenaphthene, acenocoumarol, acetohexamide, acetomeroctol, acetoxolone, acetyldigitoxins, acetylene dibromide, acetylene dichloride, acetylsalicylic acid, alantolactone, aldrin, alexitol sodium, allethrin, allylestrenol, allyl sulfide, alprazolam, aluminum bis(acetylsalicylate), ambucetamide, aminochlothenoxazin, aminoglutethimide, amyl chloride, androstenediol, anethole trithone, anilazine, anthralin, Antimycin A, aplasmomycin, arsenoacetic acid, asiaticoside, astemizole, aurodox, aurothioglycanide, 8-azaguanine, azobenzene;

baicalein, Balsam Peru, Balsam Tolu, barban, baxtrobin, bendazac, bendazol, bendroflumethiazide, benomyl, benzathine, benzestrol, benzodepa, benzoxiquinone, benzphetamine, benzthiazide, benzyl benzoate, benzyl cinnamate, bibrocathol, bifenox, binapacryl, bioresmethrin, bisabolol, bisacodyl, bis(chlorophenoxy)methane, bismuth iodosubgallate, bismuth subgallate, bismuth tannate, Bisphenol A, bithionol, bomyl, bromoisovalerate, bomyl chloride, bomyl isovalerate, bornyl salicylate, brodifacoum, bromethalin, broxyquinoline, bufexamac, butamirate, butethal, buthiobate, butlated hydroxyanisole, butylated hydroxytoluene;

calcium iodostearate, calcium saccharate, calcium stearate, capobenic acid, captan, carbamazepine, carbocloral, carbophenothin, carboquone, carotene, carvacrol, cephaeline, cephalin, chaulmoogfic acid, chenodiol, chitin, chlordane, chlorfenac, chlorfenethol, chlorothalonil, chlorotrianisene, chlorprothixene, chlorquinaldol, chromonar, cilostazol, cinchonidine, citral, clinofibrate, clofazimine, clofibrate, cloflucarban, clonitrate, clopidol, clorindione,

cloxazolam, coroxon, corticosterone, coumachlor, coumaphos, coumithoate cresyl acetate, crimidine, crifomate, cuprobam, cyamemazine, cyclandelate, cyclarbamate cymarin, cypennethril;

dapsone, defosfamide, deltamethrin, deoxycorticocosterone acetate, desoximetasone, dextromoramide, diacetazoto, dialifor, diathymosulfone, decapthon, dichlofluani, dichlorophen, dichlorphenamide, dicofol, dicryl, dicmarol, dienestrol, diethylstilbestrol, difenamizole, dihydrocodeinone enol acetate, dihydroergotamine, dihydromorphine, dihydrotachysterol, dimestrol, dimethisterone, dioxathion, diphenane, N-(1,2-diphenylethyl)nicofinamide, dipyrocetyl, disulfamide, dithianone, doxenitoin, drazoxolon, durapatite, edifenphos, emodin, enfenamic acid, erbon, ergocorninine, erythrityl tetranitrate, erythromycin stearate, estriol, ethaverine, ethisterone, ethyl biscomacetate, ethylhydrocupreine, ethyl menthane carboxamide, eugenol, euprocin, exalamide;

febarbamate, fenalamide, fenbendazole, fenipentol, fenitrothion, fenofibrate, fenquizone, fenthion, feprazone, flilpin, filixic acid, floctafenine, fluanisone, flumequine, fluocortin butyl, fluoxymesterone, flurothyl, flutazolam, fumagillin, 5-furfuryl-5-isopropylbarbitufic acid, fusafungine, glafenine, glucagon, glutethimide, glybuthiazole, griseofulvin, guaiacol carbonate, guaiacol phosphate, halcinonide, hematoprphyrin, hexachlorophene, hexestrol, hexetidine, hexobarbital, hydrochlorothiazide, hydrocodone, ibuproxam, idebenone, indomethacin, inositol niacinate, iobenzamic acid, iocetamic acid, iodipamide, iomeglamic acid, ipodate, isometheptene, isonoxin, 2-isovalerylindane- 1,3-dione;

josamycin, 11-ketoprogesterone, laurocapram, 3-O-lauroylpyridoxol diacetate, lidocaine, lindane, linolenic acid, liothyronine, lucensomycin, mancozeb, mandelic acid, isoamyl ester, mazindol, mebendazole, mebhydroline, mebiquine, melarsoprol, melphalan, menadione, menthyl valerate, mephenoxalone, mephentermine, mephenytoin, meprylcaine, mestanolone, mestranol, mesulfen, metergoline, methallatal, methandriol, methaqualone, 3-

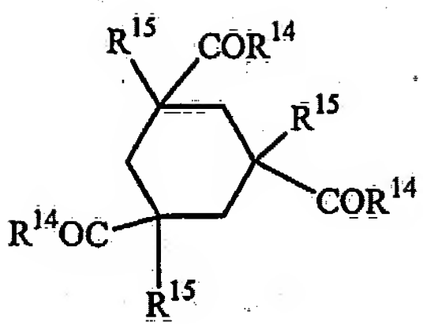
methylcholanthrene, methylphenidate, 17-methyltestosterone, metipranolol, minaprine, myoral, nafialofos, nafiopidil, naphthalene, 2-naphthyl lactate, 2-(2-naphthyloxy)ethan01, naphthyl salicylate, naproxen, nealbarbital, nemadectin, niclosamide, nicoclonate, nicomorphine, nifuroquine, nifuroxazide, nitracrine, nitromersol, nogalamycin, nordazepam, norethandrolone, norgestrienone;

octavefine, oleandrin, oleic acid, oxazepam, oxazolam, oxeladin, oxwthazaine, oxycodone, oxymesterone, oxyphenistan acetate, paclitaxel, paraherquamide, parathion, pemoline, pentaerythritol tetranitrate, pentylphenol, perphenazine, phencarbamide, pheniramine, 2-phenyl-6-chlorophenol, phentlmethylbarbituric acid, phenytoin, phosalone, phthalylsulfathiazole, phylloquinone, picadex, pifarnine, piketopfen, piprozolin, pirozadil, plafibride, plaunotol, polaprezinc, polythiazide, probenecid, progesterone, promegestone, propanidid, propargite, propham, proquazone, protionamide, pyrimethamine, pyrimithate, pyrvinium pamoate;

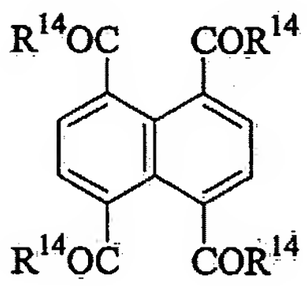
quercetin, quinbolone, quizalofo-ethyl, rafoxanide, rescinnamine, rociverine, ronnel salen, scarlet red, siccmn, simazine, simetfide, sobuzoxane, solan, spironolactone, squalene, stanolone, sucralfate, sulfabenz, sulfaguanole, sulfasalazine, SUlfoxide, sulpiride, suxibuzone, talbutal, terguide, testosterone, tetrabromocresol, tetrandrine, thiacetazone, thiocolchicine, thiocftc acid, thioquinox, thioridazine, thiram, thymyl N-isoamylcarbamate, tioxidazole, tioxolone, tocopherol, tolciclate, tolnafiate, triclosan, triflusal, triparanol;

ursolic acid, valinomycin, verapamil, vinblastine, vitamin A, vitamin D, vitamin E, xenbucin, xylazine, zaltoprofen, and zearalenone.

A specific polyacid moiety includes compounds having the formula



or



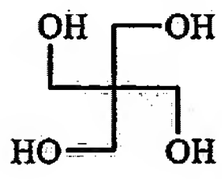
.

A specific R^{15} is alkyl.

A more specific R^{15} is methyl, ethyl, or propyl.

A more specific R^{15} is methyl, or propyl.

A specific polyol has the formula:



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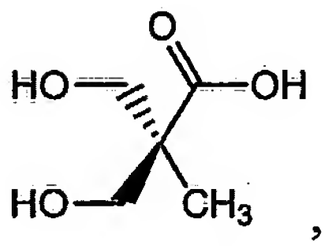
Specific R^2 groups are derived from compounds having the formula:



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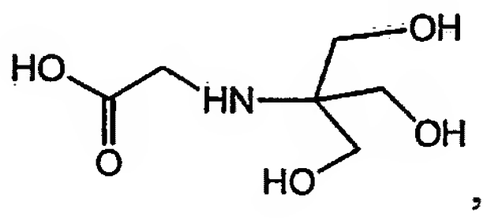

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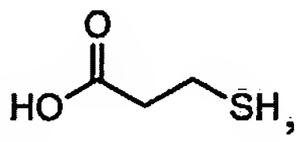

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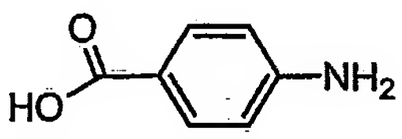
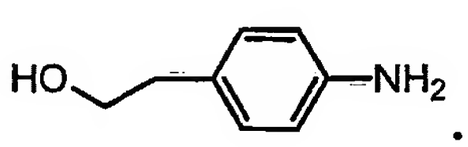


or



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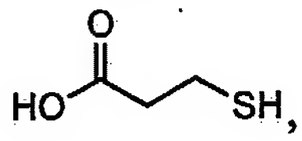
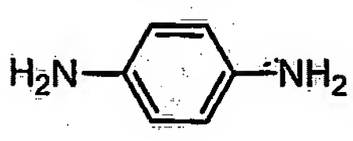
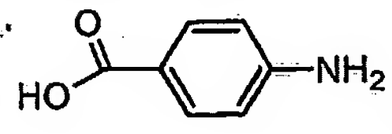
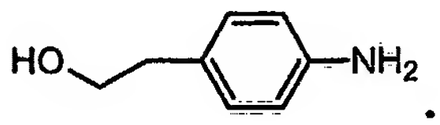
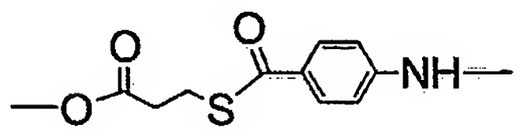
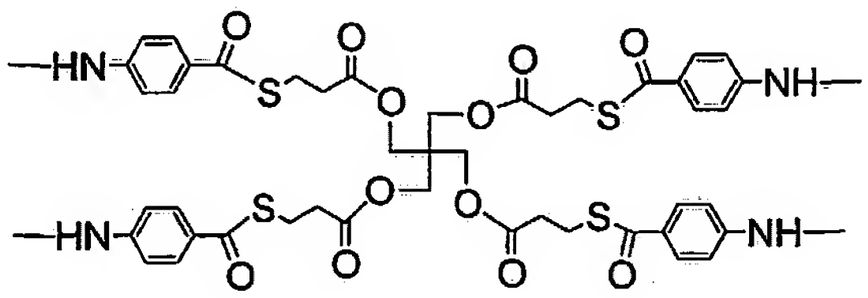
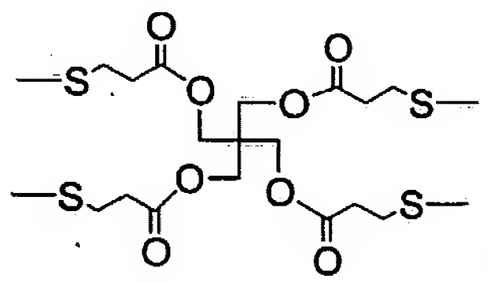
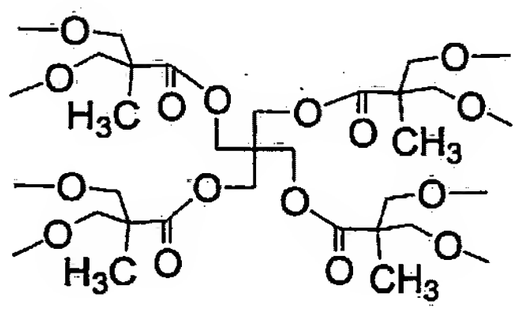
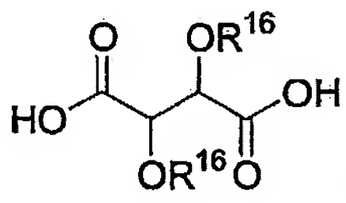
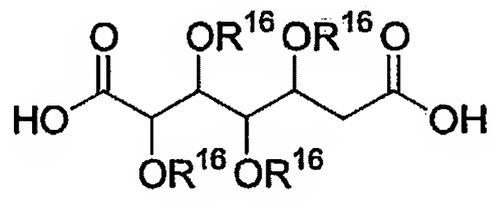
More specific R^2 groups are derived from compounds having the formula:  ,  ,  or  .

A Specific R^2 groups has the formula:,  .

A specific R^1 - R^2 combination is pentaerythritol tetrakis(3-mercapto-propionate) having the formula:

 ,  or  .

A specific R^3 group has the formula

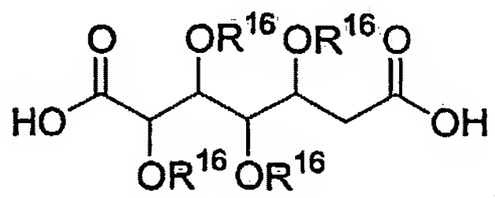
 or 

wherein each R^{16} is an alkanoyl group having from 2 to about 24 carbon atoms.

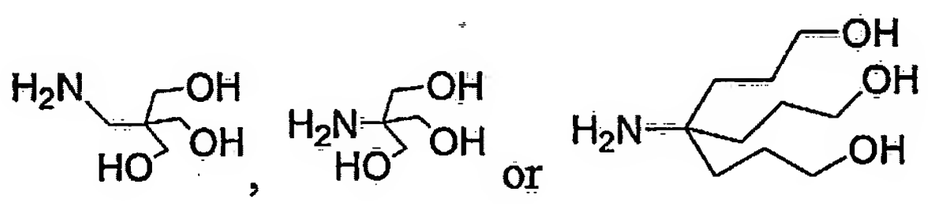
A specific R^{16} group is an alkanoyl group having from about 6 to about 18 carbon atoms.

A more specific R^{16} group is an alkanoyl group having from about 8 to about 12 carbon atoms.

A more specific R^3 group is



Specific R^4 groups are derived from compounds having the formula:



Specific R^5 groups are polyethylene ethers or polyethylene imines.

Specific polyethylene ethers have alkylene oxide units containing from 2 to about 10 carbon atoms.

Other specific polyethylene ethers have the formula $-(O\text{-}CH_2\text{-}CH_2)_f-$ where f is an integer from about 2 to about 150.

More specific polyethylene ethers have the formula $-(O\text{-}CH_2\text{-}CH_2)_f-$ where f is an integer from about 50 to about 110.

Specific polyethylene imines have units containing from 2 to about 10 carbon atoms.

Other specific polyethylene imines have the formula $-(N(R^7)\text{-}CH_2\text{-}CH_2)_f-$ where f is an integer from about 2 to about 150.

More specific polyethylene imines have the formula $-(N(R^7)\text{-}CH_2\text{=}CH_2)_f-$ where f is an integer from about 50 to about 110.

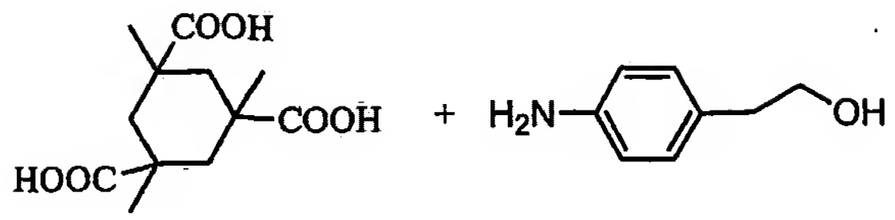
Specific R^6 group is an alkyl or aryl groups, biotin, streptavidin, sugar moieties, folic acid, amino acids and a peptides.

A more specific R^6 groups is the peptide Arg-Gly-Asp (R-G-D) or Tyr-Ile-Gly-Ser-Arg (Y-I-G-S-R).

A more specific R^6 group is biotin.

The compounds of the invention can be prepared using procedures known to those skilled in the art. A representative synthesis is illustrated in Scheme 1, below.

SCHEME 1



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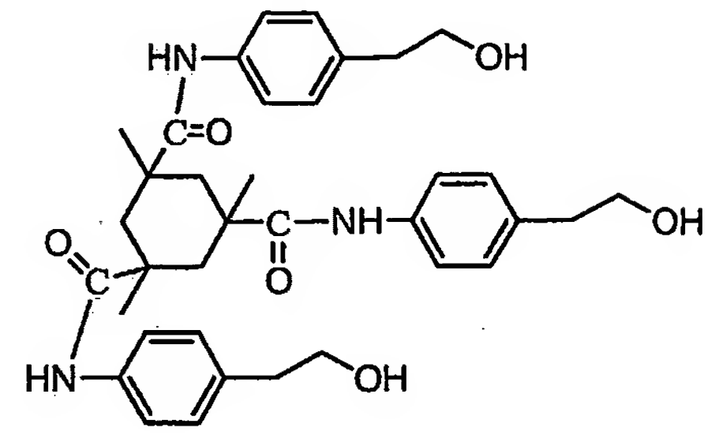
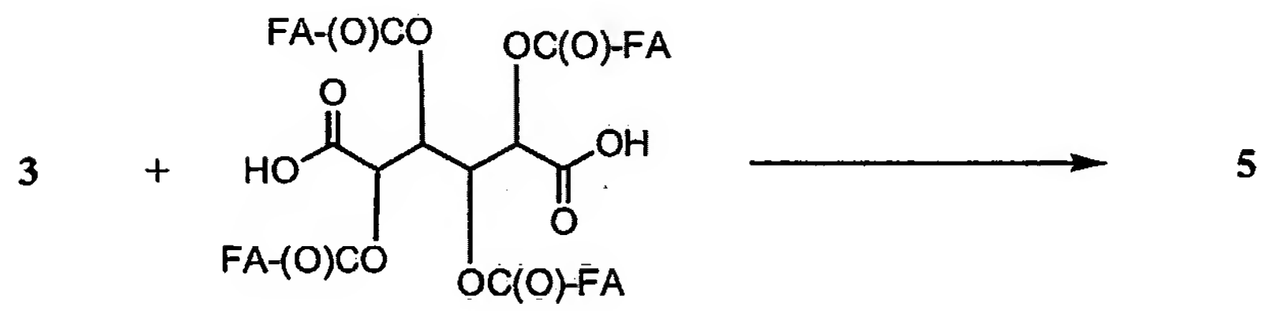
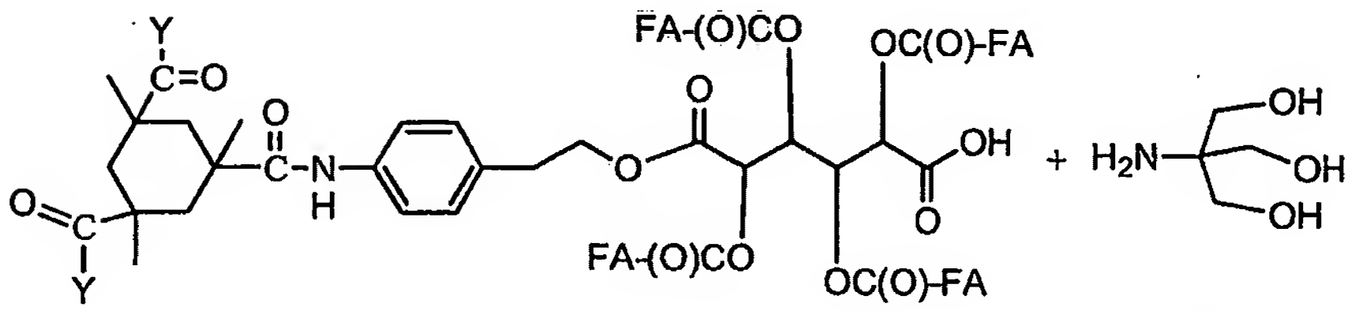


3



4 5



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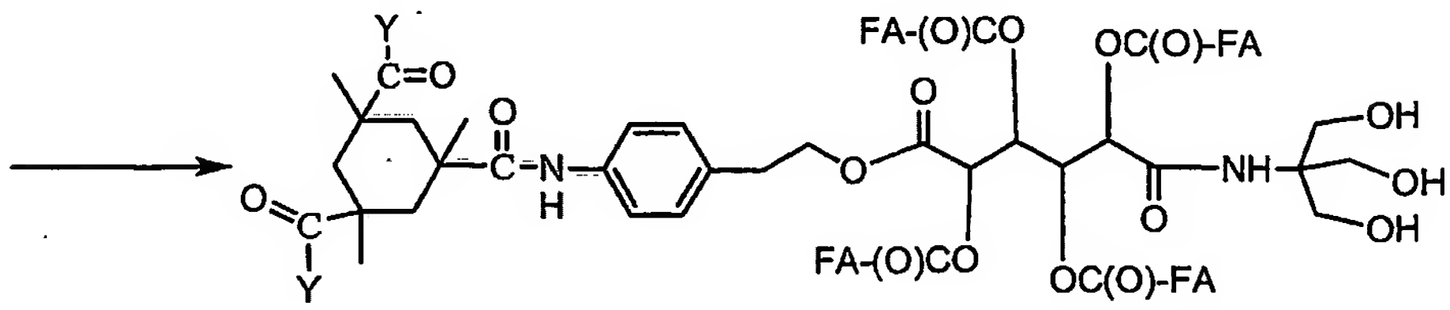
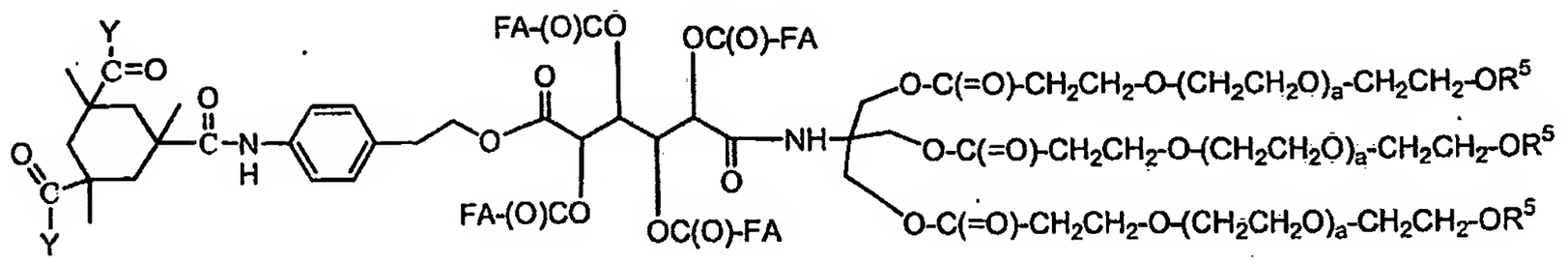


7

SCHEME 1 (cont.)

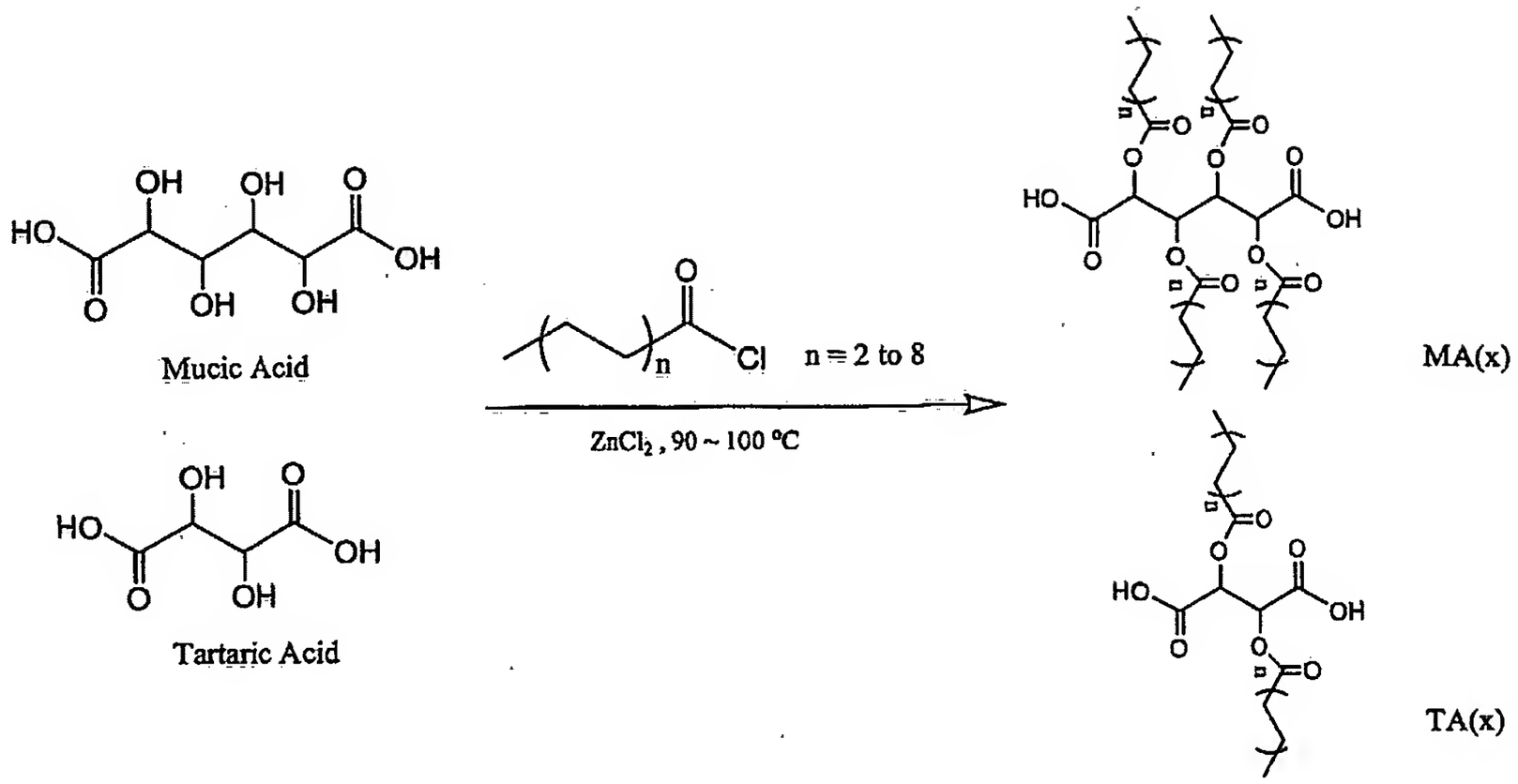
7 + $HO\text{-}C(=O)\text{-}CH_2CH_2\text{-}O\text{-}(CH_2CH_2O)_a\text{-}CH_2CH_2\text{-}OR^5$



Triacid, **1**, is reacted with three equivalents of 2-(4-amino-phenyl)-ethanol, **2**, in the presence of a coupling agent, dicyclocarbdiimide (DCC), to provide the tri-amide triol, **3**. the triol is reacted with Mucic acid fatty acid ester (FA = a fatty acid residue) to provide acid, **5**. (Each Y represents the corresponding group after completion of each reaction step.) Acid, 5, is reacted with amine triol, **6**, by activation of the carboxylic acid with DCC, to provide triol amide, **7**. Amide, **8**, is reacted with a hydrophilic group such as, a polyethylene or a polyethylene imine to provide the macromolecule, **8**.

Schemes 2 and 2A illustrate the preparation of the acylated compounds for use in R^3, the hydrophobic portion of the compounds of the invention. The acids are reacted with an acyl halide, (*e.g.*, $CH_3\text{-}(CH_2CH_2)_nC(=O)Cl$, where m is from 2 to about 8) to provide the polyacylated products. Alternatively, the acyl halide, (*e.g.*, $CH_3\text{-}(CH_2CH_2)_nC(=O)Cl$, or $CH_2=CH\text{-}(CH_2CH_2)_pC(=O)Cl$, where m is from 2 to about 8) is reacted with the acid in the presence of pyridine to provide the polyacylated compounds.

SCHEME 2



The macromolecules of the invention are particularly useful for solubilizing hydrophobic molecules, particularly therapeutic agents that are hydrophobic in nature. Thus, according to one embodiment of the present invention, a therapeutic agent is encapsulated by combining the agent and a plurality of compounds of formula (I) in a solvent, such as water. If the macromolecule has unsaturated groups, the compounds of formula (I) can be cross-linked to provide an encapsulate of the invention wherein the therapeutic agent is encapsulated in a cross-linked macromolecule.

The encapsulates of the invention that comprise a therapeutic agent can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the encapsulates of the invention may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent. They may be incorporated directly with the

food of the patient's diet. For oral therapeutic administration, the encapsulates of the invention may be used in the form of elixirs, syrups, and the like.

The compositions may also contain a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the encapsulates of the invention may be incorporated into sustained-release preparations and devices.

The encapsulates of the invention may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the encapsulates can be prepared, for example, in water. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion should be sterile, fluid and stable under the conditions of manufacture and storage. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride.

Sterile injectable solutions are prepared by incorporating the encapsulates of the invention in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by sterilization.

Encapsulation of molecules according to the invention modifies transdermal delivery of the molecule. Absorption through the skin can be increased or decreased by a factor of up to about 1000. Thus, the pharmaceutical dosage forms of present invention include dosage forms suitable for transdermal delivery, which, in addition to aqueous solutions, also include aqueous gels. The dosage form may be applied directly to the skin as a lotion, cream or salve, or a transdermal drug delivery device such as a transdermal patch may be employed, in which the encapsulated molecule is retained in the active agent reservoir of the patch.

The dose and method of administration will vary from animal to animal and be dependent upon such factors as the type of animal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular therapeutic agent employed, the specific use for which the agent is employed, and other factors which those skilled in the relevant field will recognize.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular dosage form of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of agent are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg to about 1,000 mg of therapeutic agent, per kg of animal weight. Preferred dosages range from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the dosage forms of this invention

may administered several times daily, and other dosage regimens may also be useful.

The compounds of formula (I), of the invention may also be used as thickening agents, lubricants, detergents surfactants, plasticizers and anti-fouling agents. The compounds of formula (I), of the invention may be used as an emulsifying, dispersing or stabilizing agent for dyes, cosmetics, pigment and pharmaceutical products. The compounds of formula (I), of the invention are particularly useful as an, emulsifying, dispersing or stabilizing agent in the dyeing of textiles and for encapsulating dyes for cosmetics. The compounds of formula (I), of the invention are useful as lubricants and as a thickening agents for paints. The compounds of formula (I), of the invention may also be employed as an emulsifying, dispersing or stabilizing agent for components of photographic compositions and developers.

For therapeutic applications, the preferred polymers of the invention hydrolyze into components known to be biocompatible, *e.g.*, sugars, fatty acids, amino acids and poly(ethylene glycol). This also results in low cytotoxicity of the polymer and its hydrolysis products. The poly(alkylene oxide) units enhance the immunogenicity of the encapsulate, enabling the hydrophobic molecules to evade the body's immune system, thereby increasing the circulation time of the hydrophobic molecule. This allows for effective treatment with reduced quantities of the hydrophobic molecule, which, together with the enhanced immunogenicity, prevents or reduces the severity of incidents of toxic side effects.

The following non-limiting examples set forth hereinbelow illustrate certain aspects of the invention. All parts and percentages are by weight unless otherwise noted and all temperatures are in degrees Celsius.

All PEG's were obtained from Shearwater Polymers (Birmingham, AL) and used without further purification. All other chemicals were obtained from

Aldrich (Milwaukee, WI),and used without further purification. Analytical grade solvents were used for all the reactions. Methylene chloride, tetrahydrofuran (THF), triethylamine (TEA) and dimethylsulfoxide (DMSO) were distilled. 4-(dimethylamino)pyridinium p-toluenesulfonate (DPTS) was prepared as described by J.S. Moore, S.I. Stupp *Macromolecules* **1990**, 23, 65. ^{1}H-NMR and spectra were recorded on a Varian 200 MHz or 400 MHz spectrometer. Samples (~5-10 mg/ml) were dissolved in $CDCl_3$ or THF-d_4, with the solvent used as an internal reference. IR spectra were recorded on a Mattson Series spectrophotometer by solvent casting samples onto a KBr pellet. Thermal analysis data were determined on a Perkin-Elmer Pyris 1 DSC system, samples (~10 mg) were heated under dry nitrogen gas. Data were collected at heating and cooling rates of 5 °C/min. Gel permeation chromatography (GPC) was performed on a Perkin-Elmer Series 200 LC system. Dynamic laser scattering (DSL) measurements were carried on NICOMP particle sizing systems.

EXAMPLES

Examples 1-3 Acylation of Mucic Acid

Example 1 Mucic Acid Propyl Ester

To a neat mixture of mucic acid (4.2 g, 20 mmol) and propionyl chloride (18 ml, 200 mmol) was added $ZnCl_2$ (0.28 g, 2.0 mmol). The reaction mixture was heated at reflux temperature for three hours. After cooling, diethyl ether (20 ml) was added to the reaction mixture and the solution poured onto ice chips (approximately 100 g) with stirring. Additional diethyl ether (80 ml) was added to the mixture and stirring continued for 30 minutes more. The ether portion was separated, washed with water to a neutral pH, dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was purified by recrystallization from a cosolvent system of diethyl ether and methylene chloride, collected by vacuum filtration, washed by ice cold methylene chloride

and dried at 105°C. (12 hours) to constant weight. A white solid having a T_m of 196°C was obtained at a 56% yield.

Example 2 Mucic Acid Hexyl Ester

Mucic acid hexyl ester was prepared as in Example 1, substituting caproyl chloride for propionyl chloride. A white solid having a T_m of 171°C was obtained at a yield of 68%.

Example 3 Mucic Acid Lauryl Ester

Mucic acid lauryl ester was prepared as in Example 1, substituting lauryl chloride for propionyl chloride. A white solid having a T_m of 145°C was obtained at a yield of 65%.

Examples 4-6 Preparation of Polymer Core

Example 4 Propyl Ester

The mucic acid propyl ester of Example 1(6.0 mmol) and 1,1,1-tris(4'-hydroxyphenyl)ethane (0.51 g, 1.7 mmol) were dissolved in anhydrous ethyl ether (150 ml). To the reaction mixture, a solution of DCC (1.2 g, 6.0 mmol) and DMAP (0.74 g, 6.0 mmol) in 25 ml methylene chloride was added dropwise. After 15 minutes, the DCC side-product (dicyclohexylurea) was removed by suction filtration. The filtrate was washed with 20 ml portions of 0.1 N HCL (2x) and brine (4x), dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude product was purified by flash chromatography using ethyl ether: methanol: acetic acid (90:5:5) as eluent. A white solid having a T_m of 158°C was obtained at 58% yield.

Example 5 Hexyl Ester

The hexyl ester core molecule was prepared according to the method of Example 4, substituting the mucic acid hexyl ester of Example 2 for the mucic

acid propyl ester. A white solid having a T_m of 147°C was obtained at 36% yield.

Example 6 Lauryl Ester

The lauryl ester core molecule was prepared according to the method of Example 4, substituting the mucic acid lauryl ester of Example 3 for the mucic acid propyl ester. A white solid having a T_m of 136°C was obtained at yield of 33%.

Examples 7-11 Preparation of Final Polymers

Example 7 Mucic Acid Hexyl Ester Core Polymer With Triethylene Glycol (TEG) Branches

To a mixture of the core molecule of Example 5 (0.106 mmol) and methoxy-terminated triethylene glycol amine (0.351 mmol) in 20 ml of methylene chloride at room temperature, DCC (0.351 mmol) and DMAP (0.351 mmol) in 2 ml methylene chloride was added dropwise. After three days, the reaction mixture was evaporated to dryness, the residue dissolved into 20 ml methanol, and the crude product precipitated from 400 ml petroleum ether at room temperature. The crude product was first purified by flash chromatography using ethyl ether: methanol: acetic acid (90:5:5) as eluent, then further purified by repetitive precipitation using methylene chloride as solvent and diethyl ether/petroleum ether as non-solvent. The ratio between methylene chloride and ethers was progressively changed. A white solvent was obtained having a T_m of 31°C, a T_d of 220°C and M_W of 2,400 daltons at a yield of 15%.

Example 8 Mucic Acid Hexyl Ester Core Polymer With PEG 2000 Branches

A mucic acid hexyl ester core polymer with PEG 2000 branches was prepared according to the method of Example 7, substituting methoxy-terminated poly(ethylene glycol) amine (H_2N-m-PEG 2000, M_w=2000) for the

methoxy-terminated triethylene glycol amine of Example 7. A white solid was obtained having a T_m of 54°C and a M_w of 9,400 daltons at a yield of 25%.

Example 9 Mucic Acid Hexyl Ester Core Polymer With PEG 5000 Branches

A mucic acid hexyl ester core polymer with PEG 5000 branches was prepared according to the method of Example 7, substituting methoxy-terminated poly(ethylene glycol) amine (H_2N-PEG 5000, M_w=5000) for the methoxy-terminated triethylene glycol amine of Example 7. A white solid having a T_m of 61°C and a M_w of 17,800 daltons was obtained at 17% yield.

Example 10 Mucic Acid Propyl Ester Core Polymer With PEG 5000 Branches

Mucic acid propyl ester core polymer with PEG 5000 branches was prepared according to the method of Example 9, substituting the mucic acid propyl ester core polymer of Example 4 for the mucic acid hexyl ester core polymer. A white solid was obtained having a T_m of 62°C and a M_w of 17,000 daltons at 30% yield.

Example 11 Mucic Acid Lauryl Ester Core Polymer With PEG 5000 Branches

Mucic acid lauryl ester core polymer with PEG 5000 branches was prepared according to the method of Example 9, substituting the mucic acid lauryl ester core polymer of Example 6 for the mucic acid hexyl ester core polymer. A white solid was obtained having a T_m of 60°C and a M_w of 19,100 daltons at a yield of 45%.

For the polymers of Examples 8-11, TGA showed two stages of decomposition. The first stage corresponded to cleavage of the core structures from the ethylene oxide chains (about 200°C.) with the appropriate weight loss, and the second stage corresponded to decomposition of the ethylene oxide chain.

Example 12 Encapsulation Studies

Lidocaine (50 mg) and the polymer of Example 9 (50 mg) were dissolved in 2.0 ml methylene chloride. The solution was evaporated to dryness and the solid residue extensively washed with hexane until lidocaine was no longer detected in the washings. The solid was dried under vacuum at 25°C for about 2 hours. A portion (5.0 mg) of this solid was dissolved into methanol (1.0 ml) to release the entrapped lidocaine, and the lidocaine concentration was quantified by high pressure liquid chromatography (HPLC) according to a calibration curve generated from a series of standard solutions ranging from 0.005 to 0.5 mg/ml lidocaine. The linearity of the curve indicated a direct, proportional relationship between absorbance and lidocaine concentration. Using the equation of the lidocaine calibration curve, the amount of lidocaine entrapped in the unimolecular micelle core was determined. PEG with a molecular weight of 5,000 daltons was used as the HPLC control.

Encapsulation number was defined as the amount of molecules that can be entrapped within the polymeric micelles. The values for the polymers of Example 9, 10 and 11 were 1.0, 0.7 and 1.6 weight %, respectively. The encapsulation number increased as the hydrophobicity of the polymer interior increased.

The PEG arms of the polymers of the present invention thus form a hydrophilic shell that solubilizes the polymer in water, while the core forms a hydrophobic microenvironment that encapsulates small hydrophobic molecules. Unlike conventional micelles, however, the polymeric micelles of the present invention are thermodynamically stable because of the covalent linkages between the polymer arms. The ability to encapsulate small molecules, the enhanced solubility and the lack of aggregation characterize the usefulness of these polymers as drug delivery systems. Candidate drugs, of which there are many, have aromatic or heteroaromatic moieties and carbonyl functionalities (e.g., amides and carboxylates). The biocompatibility and biodegradability of

these polymers further characterize their utility for drug delivery. The excellent water-solubility of these polymers makes intravenous injection and oral administration of hydrophobic drug molecules possible. For controlled release applications, the small size of these polymers, along with their enhanced thermodynamic stability, further characterizes their utility.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

Claims:

1. A compound having formula (I):

$$R^1\text{-}((R^2)_a\text{-}(R^3)_b\text{-}(R^4)_c\text{-}(R^5)_d\text{-}(R^6)_e)_n \qquad (I)$$

wherein R^1 is a core comprising a polyol or polyacid;

each R^2 independently is a divalent or polyvalent group having the formula $-X^1\text{-}R^8\text{-}(X^{1a})_g$-, wherein X^1 and X^{1a} are independently -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)- or absent, and each R^8 is independently -($C_{1\text{-}8}$)alkylene-, branched -($C_{1\text{-}8}$)alkylene- or -($C_{6\text{-}10}$)aryl-; a is 0 or an integer from 1 to about 10; and g is an integer from 1 to about 6;

each R^3 independently is a divalent dicarboxylic acid moiety having the formula -C(=O)-R^9-C(=O)-, wherein R^9 is an alkylene or cycloalkylene group containing from 1 to about 15 carbon atoms, substituted with a total of from 1 to about 10 hydroxy groups, wherein one or more of the hydroxy groups of the dicarboxylic acid are acylated with an acid residue; and b is an integer from 1 to about 10;

each R^4 independently is a divalent or polyvalent group having the formula $-X^2\text{-}R^{10}\text{-}(X^{2a})_h$-, wherein X^2 is -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; X^{2a} is -C(=O)-, -C(=S)-, –O–, –S–, or –N(R^7)– and R^{10} is -($C_{1\text{-}8}$)alkylene-, branched -($C_{1\text{-}8}$)alkylene- or -($C_{6\text{-}10}$)aryl-; and c is 0 or an integer from 1 to about 10; and h is an integer from 1 to 6;

each R^5 independently is a group having the formula:

$$-R^{12}\text{-}(R^{11})_f\text{-}R^{12}\text{-}X^3\text{-}$$

wherein R^{11} is a sugar moiety; or a poly(alkylene oxide) or poly(alkylene imine) group having the formula -(–X^4–R^{13})-; wherein R^{13} is -($C_{2\text{-}40}$)alkylene- or branched -($C_{3\text{-}40}$)alkylene-; wherein each X^3 is independently -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; each X^4

is independently –O–, or –N(R^7)-; and f is an integer from about 2 to about 150; and d is from 1 to about 6;

each R^{12} is independently a bond, -(C_{1-40})alkylene- or branched -(C_{1-40})alkylene- groups, wherein each R^{12} is optionally substituted with one or more (e.g., 1, 2, or 3) functional group; and X^4 is -O-, -S-, or –N(R^7)-;

wherein n is from 2 to 12; provided that a and b are not both zero;

wherein each R^7 is independently selected from the group consisting of hydrogen, and $C_{(1-40)}$alkyl group, where the alkyl group can be a straight-chain or branched group; and R^a and R^b are each independently hydrogen (C_{1-8})alkyl, aryl, aryl(C_{1-8})alkylene; and

R^6 is hydrogen, are –OH, –OR^a, –NR^aR^b, -CO_2H, -SO_3H (sulfo), –CH_2–OH, –CH_2–OR^a, -CH_2-O-CH_2-R^a,–CH_2–NR^aR^b or a targeting moiety; provided that at least one R^6 group is a targeting moiety; and e is from 1 to about 6.

2. A compound having formula (I):

$$R^1\text{-}((R^2)_a\text{-}(R^3)_b\text{-}(R^4)_c\text{-}(R^5)_d\text{-}(R^6)_e)_n \qquad (I)$$

wherein R^1 is a core comprising a polyol or polyacid;

each R^2 independently is a divalent or polyvalent group having the formula –X^1-R^8-(X^{1a})$_g$-, wherein X^1 and X^{1a} are independently -C(=O)-, –C(=S)-, –O–, –S–, -N(R^7)- or absent, and each R^8 is independently -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; a is an integer from 1 to about 10; and g is an integer from 1 to about 6;

each R^3 independently is a divalent dicarboxylic acid moiety having the formula -C(=O)-R^9-C(=O)-, wherein R^9 is an alkylene or cycloalkylene group containing from 1 to about 15 carbon atoms, substituted with a total of from 1 to about 10 hydroxy groups, wherein

one or more of the hydroxy groups of the dicarboxylic acid are acylated with an acid residue; and b is an integer from 1 to about 10;

each R^4 independently is a divalent or polyvalent group having the formula $–X^2-R^{10}-(X^{2a})_h-$, wherein X^2 is -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; X^{2a} is -C(=O)-, -C(=S)-, –O–, –S–, or –N(R^7)– and R^{10} is -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; and c is 0 or an integer from 1 to about 10; and h is an integer from 1 to 6;

each R^5 independently is a group having the formula:

$$-R^{12}-(R^{11})_f-R^{12}-X^3-$$

wherein R^{11} is a sugar moiety; or a poly(alkylene oxide) or poly(alkylene imine) group having the formula -(–X^4–R^{13})-; wherein R^{13} is -(C_{2-40})alkylene- or branched -(C_{3-40})alkylene-; wherein each X^3 is independently -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; each X^4 is independently –O–, or –N(R^7)-; and f is an integer from about 2 to about 150; and d is from 1 to about 6;

each R^{12} is independently a bond, -(C_{1-40})alkylene- or branched -(C_{1-40})alkylene- groups, wherein each R^{12} is optionally substituted with one or more (e.g., 1, 2, or 3) functional groups; and X^4 is -O-, -S-, or –N(R^7)-;

wherein n is from 2 to 12; provided that a and b are not both zero; wherein each R^7 is independently selected from the group consisting of hydrogen, and $C_{(1-40)}$alkyl group, where the alkyl group can be a straight-chain or branched group; and R^a and R^b are each independently hydrogen (C_{1-8})alkyl, aryl, aryl(C_{1-8})alkylene; and

R^6 is hydrogen, are –OH, –OR^a, –N$R^a R^b$, -CO_2H, -SO_3H (sulfo), –CH_2–OH, –CH_2–OR^a, -CH_2-O-CH_2-R^a,–CH_2–N$R^a R^b$ or a targeting moiety; and e is from 1 to about 6.

3. A compound having formula (I):

$$R^1\text{-}((R^2)_a\text{-}(R^3)_b\text{-}(R^4)_c\text{-}(R^5)_d\text{-}(R^6)_e)_n \qquad (I)$$

wherein R^1 is a core comprising a polyol or polyacid;

each R^2 independently is a divalent or polyvalent group having the formula $-X^1\text{-}R^8\text{-}(X^{1a})_g\text{-}$, wherein X^1 and X^{1a} are independently -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)- or absent, and each R^8 is independently -($C_{1\text{-}8}$)alkylene-, branched -($C_{1\text{-}8}$)alkylene- or -($C_{6\text{-}10}$)aryl-; a is 0 or an integer from 1 to about 10; and g is an integer from 1 to about 6;

each R^3 independently is a divalent dicarboxylic acid moiety having the formula -C(=O)-R^9-C(=O)-, wherein R^9 is an alkylene or cycloalkylene group containing from 1 to about 15 carbon atoms, substituted with a total of from 1 to about 10 hydroxy groups, wherein one or more of the hydroxy groups of the dicarboxylic acid are acylated with an acid residue; and b is an integer from 1 to about 10;

each R^4 independently is a divalent or polyvalent group having the formula $-X^2\text{-}R^{10}\text{-}(X^{2a})_h\text{-}$, wherein X^2 is -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; X^{2a} is -C(=O)-, -C(=S)-, –O–, –S–, or –N(R^7)– and R^{10} is -($C_{1\text{-}8}$)alkylene-, branched -($C_{1\text{-}8}$)alkylene- or -($C_{6\text{-}10}$)aryl-; and c is 0 or an integer from 1 to about 10; and h is an integer from 1 to 6;

each R^5 independently is a group having the formula:

$$-R^{12}\text{-}(R^{11})_f\text{-}R^{12}\text{-}X^3\text{-}$$

wherein R^{11} is a sugar moiety; or a poly(alkylene oxide) or poly(alkylene imine) group having the formula -(–X^4–R^{13})-; wherein R^{13} is -($C_{2\text{-}40}$)alkylene- or branched -($C_{3\text{-}40}$)alkylene-; wherein each X^3 is independently -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; each X^4 is independently –O–, or –N(R^7)-; and f is an integer from about 2 to about 150; and d is from 1 to about 6;

each R^{12} is independently a bond, -($C_{1\text{-}40}$)alkylene- or branched -($C_{1\text{-}40}$)alkylene- groups, wherein each R^{12} is optionally substituted with

one or more (e.g., 1, 2, or 3) functional groups; and X^4 is -O-, -S-, or –$N(R^7)$-;

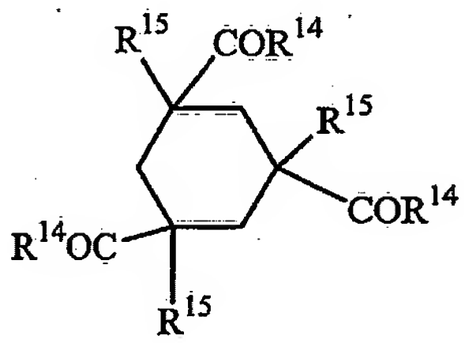
wherein n is from 2 to 12; provided that a and b are not both zero; wherein each R^7 is independently selected from the group consisting of hydrogen, and $C_{(1-40)}$alkyl group, where the alkyl group can be a straight-chain or branched group; and R^a and R^b are each independently hydrogen (C_{1-8})alkyl, aryl, aryl(C_{1-8})alkylene; and

R^6 is hydrogen, are –OH, –OR^a, –NR^aR^b, -CO_2H, -SO_3H (sulfo), –CH_2–OH, –CH_2–OR^a, -CH_2-O-CH_2-R^a,=CH_2–NR^aR^b or a targeting moiety; and e is from 1 to about 6.

4. A compound having formula (I):

$$R^1\text{-}((R^2)_a\text{-}(R^3)_b\text{-}(R^4)_c\text{-}(R^5)_d\text{-}(R^6)_e)_n \qquad (I)$$

wherein R^1 is a core comprising a polyacid moiety having the formula



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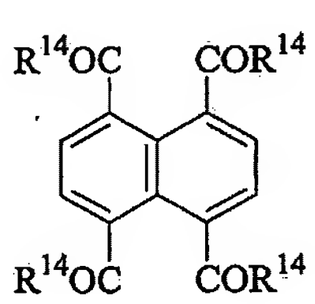
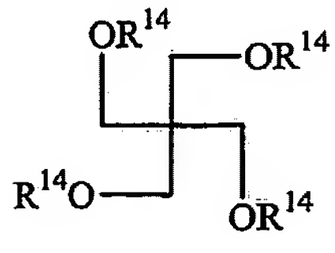


or a pentaerythritol polyol having the formula


;

wherein each R^2 independently is a divalent or polyvalent group having the formula $-X^1-R^8-(X^{1a})_g-$, wherein X^1 and X^{1a} are independently -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)- or absent, and each R^8 is independently -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; a is 0 or an integer from 1 to about 10; and g is an integer from 1 to about 6;

each R^3 independently is a divalent dicarboxylic acid moiety having the formula -C(=O)-R^9-C(=O)-, wherein R^9 is an alkylene or cycloalkylene group containing from 1 to about 15 carbon atoms, substituted with a total of from 1 to about 10 hydroxy groups, wherein one or more of the hydroxy groups of the dicarboxylic acid are acylated with an acid residue; and b is an integer from 1 to about 10;

each R^4 independently is a divalent or polyvalent group having the formula $-X^2-R^{10}-(X^{2a})_h-$, wherein X^2 is -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; X^{2a} is -C(=O)-, -C(=S)-, –O–, –S–, or –N(R^7)– and R^{10} is -(C_{1-8})alkylene-, branched -(C_{1-8})alkylene- or -(C_{6-10})aryl-; and c is 0 or an integer from 1 to about 10; and h is an integer from 1 to 6;

each R^5 independently is a group having the formula:

$$-R^{12}-(R^{11})_f-R^{12}-X^3-$$

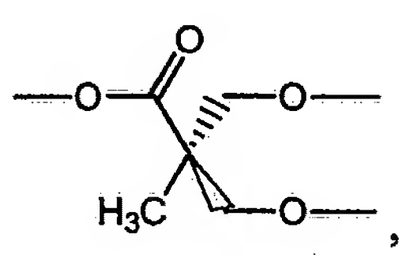
wherein R^{11} is a sugar moiety; or a poly(alkylene oxide) or poly(alkylene imine) group having the formula -(–X^4–R^{13})-; wherein R^{13} is -(C_{2-40})alkylene- or branched -(C_{3-40})alkylene-; wherein each X^3 is independently -C(=O)-, –C(=S)-, –O–, –S–, –N(R^7)– or absent; each X^4 is independently –O–, or –N(R^7)-; and f is an integer from about 2 to about 150; and d is from 1 to about 6;

each R^{12} is independently a bond, -(C_{1-40})alkylene- or branched -(C_{1-40})alkylene- groups, wherein each R^{12} is optionally substituted with one or more (e.g., 1, 2, or 3) functional groups; and X^4 is -O-, -S-, or –N(R^7)-;

wherein n is from 2 to 12; provided that a and b are not both zero; wherein each R^7 is independently selected from the group consisting of hydrogen, and $C_{(1-40)}$alkyl group, where the alkyl group can be a straight-chain or branched group; and R^a and R^b are each independently hydrogen (C_{1-8})alkyl, aryl, aryl(C_{1-8})alkylene; and

R^6 is hydrogen, are –OH, –OR^a, –NR^aR^b, -CO_2H, -SO_3H (sulfo), –CH_2–OH, –CH_2–OR^a, -CH_2-O-CH_2-R^a,–CH_2–NR^aR^b or a targeting moiety; and e is from 1 to about 6.

5. The compound of any one of claims 1-4, wherein R^2 has the formula: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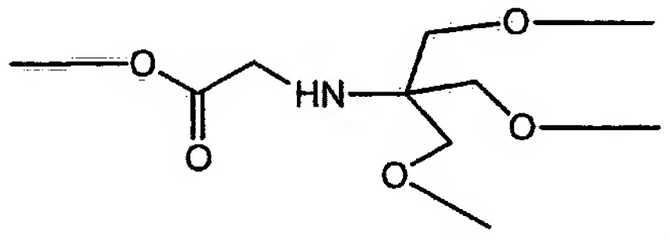
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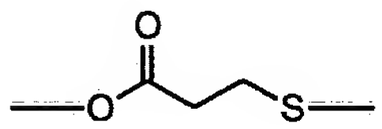
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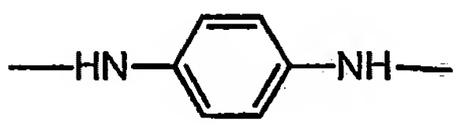
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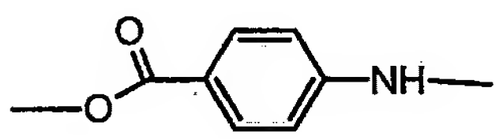
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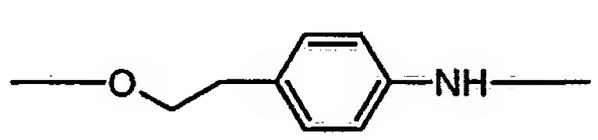
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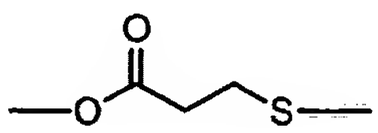
6. The compound of any one of claims 1-5, wherein R^2 has the formula: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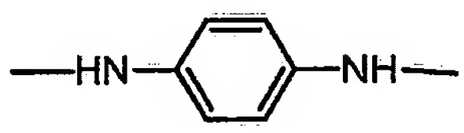
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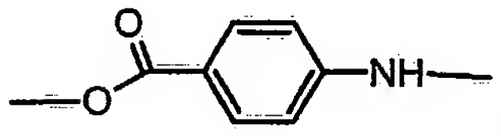
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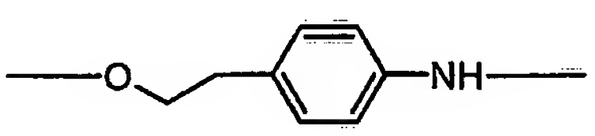
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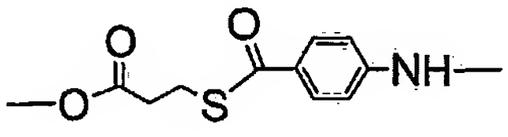
7. The compound of any one of claims 1-6, wherein R^2 has the formula: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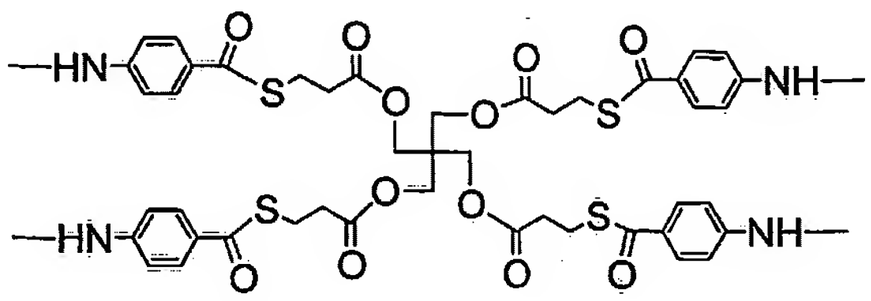
8. The compound of any one of claims 1-7, wherein the R^1–R^2 combination has the formula:



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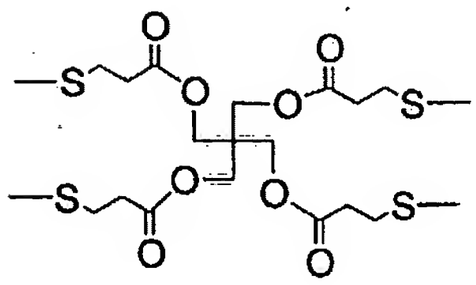

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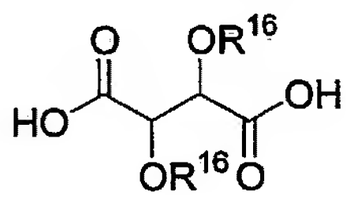
9. The compound of any one of claims 1-8, wherein R^3 has the formula



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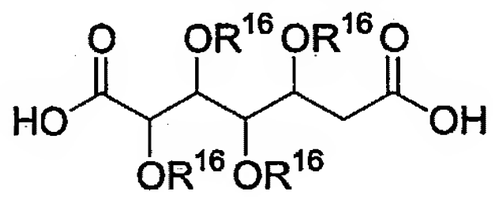
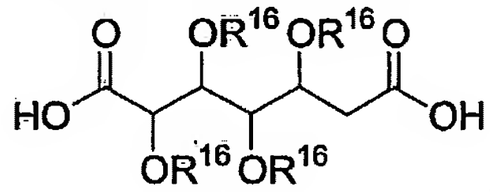


wherein each R^{16} is an alkanoyl group having from 2 to about 24 carbon atoms.

10. The compound of any one of claims 1-9, wherein R^3 is



.

11. The compound of any one of claims 1-10, wherein R^{16} is an alkanoyl group having from about 6 to about 18 carbon atoms.

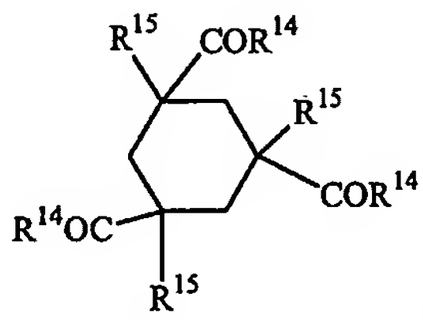
12. The compound of any one of claims 1-11, wherein R^1 has from about 2 carbons to about 20 carbons.

13. The compound of any one of claims 1-12, wherein R^1 has from about 3 carbons to about 12 carbons.

14. The compound of any one of claims 1-13, wherein the R^1 moeity has from about 4 carbons to about 10 carbons.

15. The compound of any one of claims 1-3 or 5-14, wherein R^1 is a cycloaliphatic polyol.

16. The compound of any one of claims 1-15, wherein R^1 is a polyacid having the formula



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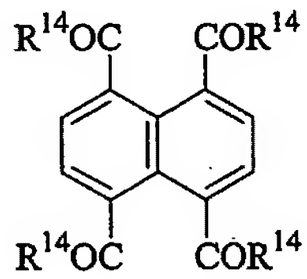
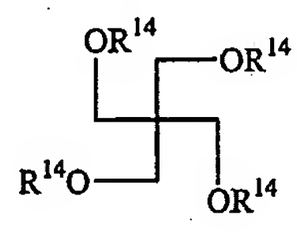


or a polyol having the formula



;

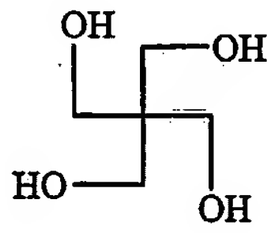
wherein each R^{14} is $-(R^2)_a-(R^3)_b-(R^4)_c-(R^5)_d-(R^6)_e$; and wherein R^{15} is hydrogen or (C_{1-6})alkyl; and R^2, R^3, R^4, R^5 , a, b, c, and d, are as defined hereinabove.

17. The compound of claim 16, where R^{15} is alkyl.

18. The compound of claim 17, where R^{15} is methyl, ethyl , or propyl.

19. The compound of claim 18, where R^{15} is methyl, or propyl.

20. The compound of any one of claims 1-16, wherein R^1 comprises a core having the formula:



21. The compound of any one of claims 1-20, wherein R^2 is –C(=O)-CH_2-CH_2-S-.

22. The compound of any one of claims 1-16 or 20-21, wherein the R^1–R^2 combination is pentaerythritol tetrakis(3-mercaptopropionate).

23. The compound of any of claims 1-16 or 20-22, wherein the R^1 moeity comprises from about 2 to about 20 hydroxy groups.

24. The compound of any one of claims 1-16 or 20-23, wherein the R^1 moeity comprises from about 2 to about 12 hydroxy groups.

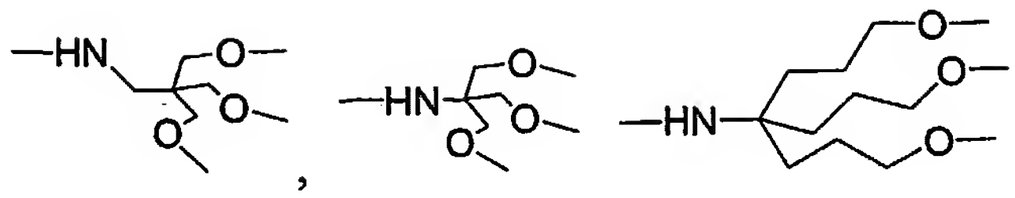
25. The compound of any one of claims 1-16 or 20-24, wherein the R^1 moeity comprises from about 2 to about 10 hydroxy groups.

26. The compound of any one of claims 1-25, wherein the R^1 moeity is substituted with one or more carboxy groups.

27. The compound of any of claims 1-26, wherein the R^1 moeity is substituted with two carboxy groups.

28. The compound of any one of claims 1-27,wherein the R^1 moeity is substituted with one carboxy group.

29. The compound of any one of claims 1-28, wherein R^4 has the formula:



30. The compound of any one of claims 1-29, wherein R^5 has the formula:

$$-R^{12}-(O-R^{13})_f-R^{12}-,$$

wherein R^{13} is a 1 to 20 carbon straight-chain or branched alkyl group,

wherein each R^{12} is optionally substituted with one or more functional groups selected from the group consisting of –OH, $–OR^a$, $–NR^aR^b$, $-CO_2H$, $-SO_3H$, $–CH_2–OR^a$, $-CH_2-O-CH_2-R^a$, $–CH_2CO_2H$, $–CH_2SO_3H$, $-O-C(=O)-CH_2-CH_2-C(=O)-O-$ or $-CH_2–NR^aR^b$;

Q is -O-, -S-, and $–NR^a-$; and

R^{12} is a 1 to 10 carbon straight-chain or branched divalent alkylene group;

R^a and R^b are each independently hydrogen (C_{1-6})alkyl, aryl, aryl(C_{1-8})alkylene

f is an integer from 2 to 150, inclusive.

31. The compound of any one of claims 1-31, wherein the R^5 is a polyethylene ether having between about 2 and about 110 alkylene oxide repeating units.

32. The compound of any one of claims 1-31, wherein the alkylene oxide units containing from 2 to about 10 carbon atoms and may be straight chained or branched.

33. The compound of any one of claims 1-31, wherein the alkylene oxide units contain from 2 to 4 carbon atoms and may be straight chained or branched.

34. The compound of any one of claims 1-31 wherein R^5 is linked to R^1 through an ester, thioester, or amide linkage.

35. The compound of any one of claims 1-31 wherein R^5 is linked to R^1 through an ester or amide linkage.

36. The compound of any one of claims 1-29, wherein R^5 has the formula:

$$-R^{12}-(N(R^7)-R^{13})_f-R^{12}-,$$

wherein each R^{12} and R^{13} are independently a 1 to 20 carbon straight-chain or branched alkyl group,

wherein each R^{12} is optionally substituted with one or more functional groups selected from the group consisting of –OH, $–OR^a$, $–NR^aR^b$, $-CO_2H$, $-SO_3H$, $–CH_2–OR^a$, $-CH_2-O-CH_2-R^a$, $–CH_2CO_2H$, $–CH_2SO_3H$, $-O-C(=O)-CH_2-CH_2-C(=O)-O-$ or $-CH_2–NR^aR^b$;

Q is -O-, -S-, and $–NR^a-$; and

R^{12} is a 1 to 10 carbon straight-chain or branched divalent alkylene group;

R^a and R^b are each independently hydrogen (C_{1-6})alkyl, aryl, aryl(C_{1-8})alkylene

f is an integer from 2 to 150, inclusive.

37. The compound of any one of claims 1-29 or 36, wherein R^5 is a polyethylene imine having between about 2 and about 110 repeating units.

38. The compound of any one of claims 1-29 or 36-37, wherein the polyethylene imine has units contain from 2 to about 10 carbon atoms.

39. The compound of any one of claims 1-38, wherein R^6 is alkyl, aryl, biotin, streptavidin, sugar moieties, folic acid, amino acids or peptides.

40. The compound of any one of claims 1-39, wherein is the peptide Arg-Gly-Asp (R-G-D) or Tyr-Ile-Gly-Ser-Arg (Y-I-G-S-R).

41. The compound of any one of claims 1-40, wherein R^6 is biotin

42. The compound of any one of claims 1-41, wherein the acid residue comprises from about 2 to about 24 carbon atoms.

43. The compound of any one of claims 1-42, wherein the acid residue comprises from about 6 to about 18 carbon atoms.

44. The compound of claim 1 wherein the acid residue comprises caprylic, capric, lauric, myristic, myristoleic, palmitic, palmitoleic, stearic, oleic, linoleic, eleostearic, arachidic, behenic, erucic acid, or a mixture thereof.

45. The compound of any of claims 1-44, wherein the functional groups are –OH, –ORa, –NRaRb, -CO2H, -SO3H (sulfo), –CH2–OH, –CH2–ORa, -CH2-O-CH2-Ra, or -CH2–NRaRb.

46. An encapsulate comprising a molecule surrounded or partially surrounded by at least one compound of formula (I), as described in any one of claims 1-45.

47. An encapsulate comprising a therapeutic agent surrounded or partially surrounded by at least one compound of formula (I), as described in any one of claims 1-45.

48. A composition comprising at least one compound of formula (I) as described in any one of claims 1-45 in a solvent.

49. The composition of claim 48, wherein the solvent comprises an organic solvent.

50. The composition of claim 48, wherein the solvent comprises water.

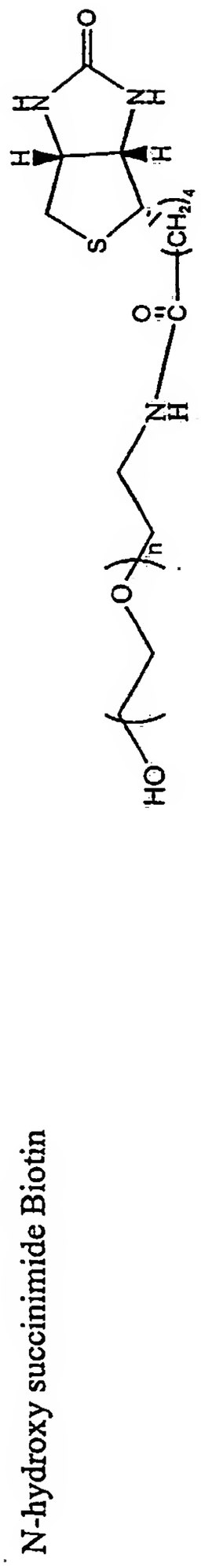
51. The composition of claim 48, wherein the solvent is water.

52. A method for preparing an encapsulate as described in claim 47, comprising combining at least one compound of formula (I), as described in any one of claims 1-45, and a molecule in a solvent; and allowing the compound of formula (I) to aggregate around the molecule, to provide the encapsulate

53. A pharmaceutical composition comprising an encapsulate as described in claim 45; and a pharmaceutically acceptable carrier.

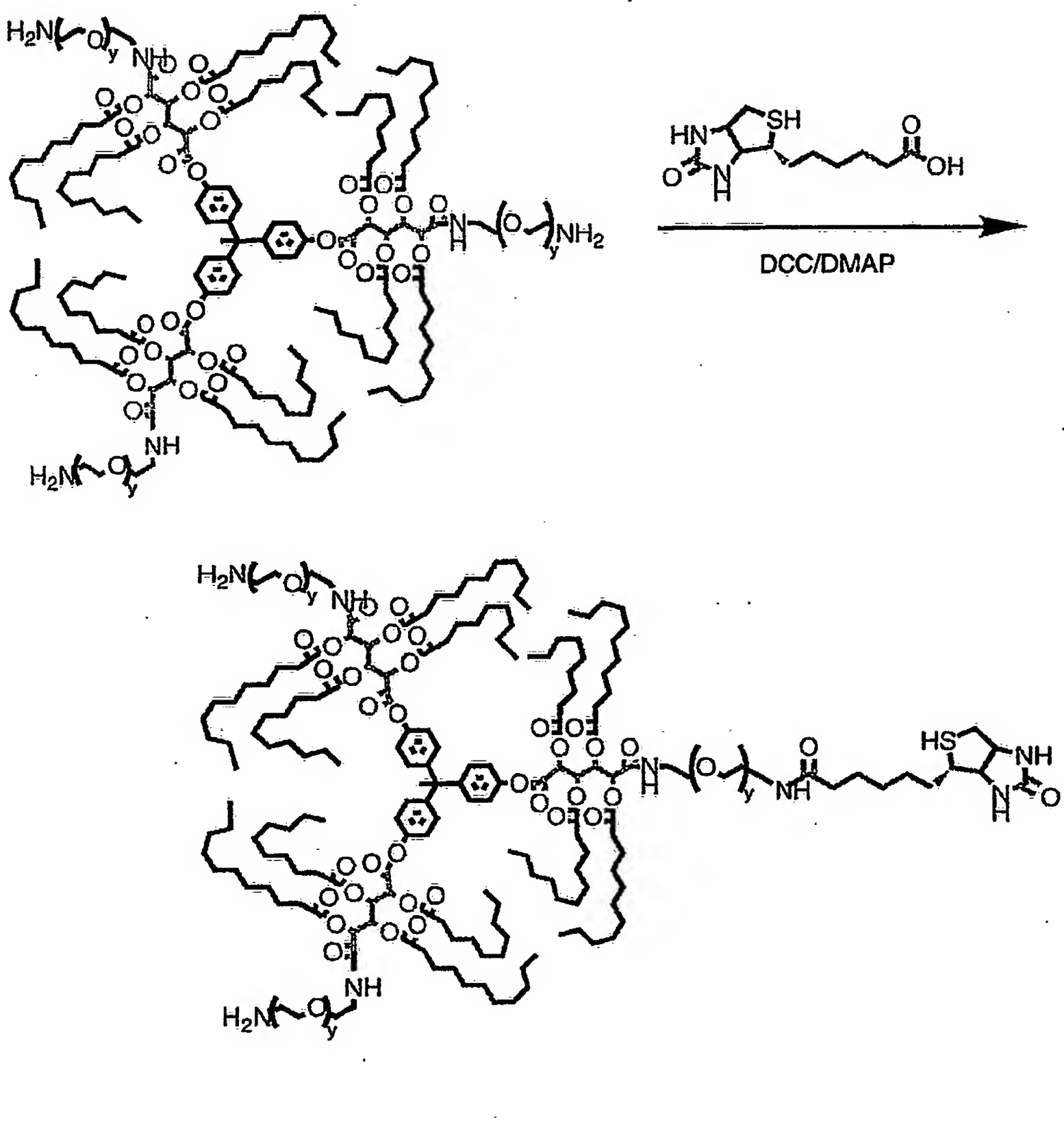
54. A method for delivering a therapeutic agent to an animal in need of treatment with the agent comprising administering an encapsulate as described in claim 45 to the animal.

Fig 1



N-hydroxy succinimide Biotin

Fig 2



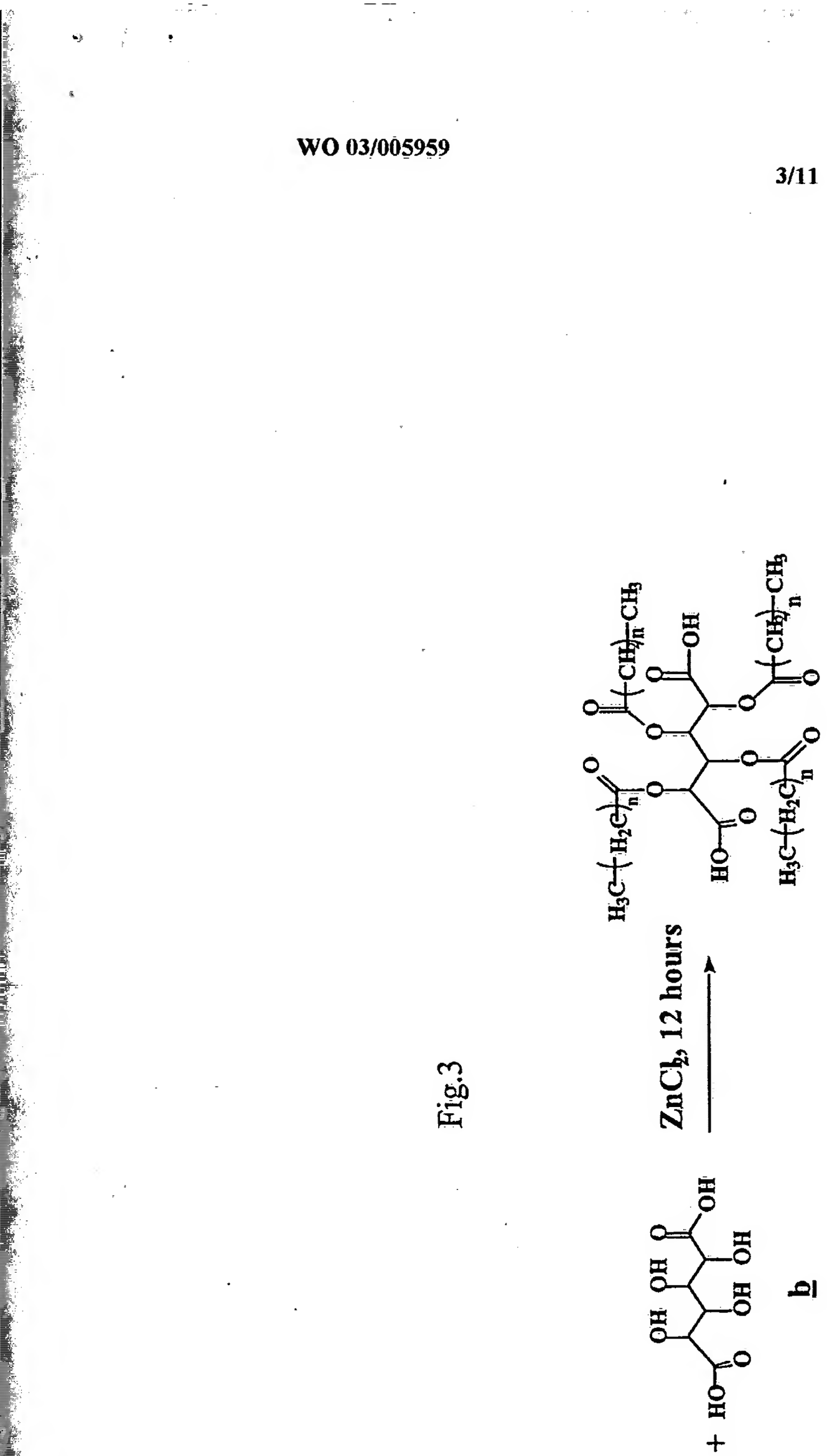


Fig.3

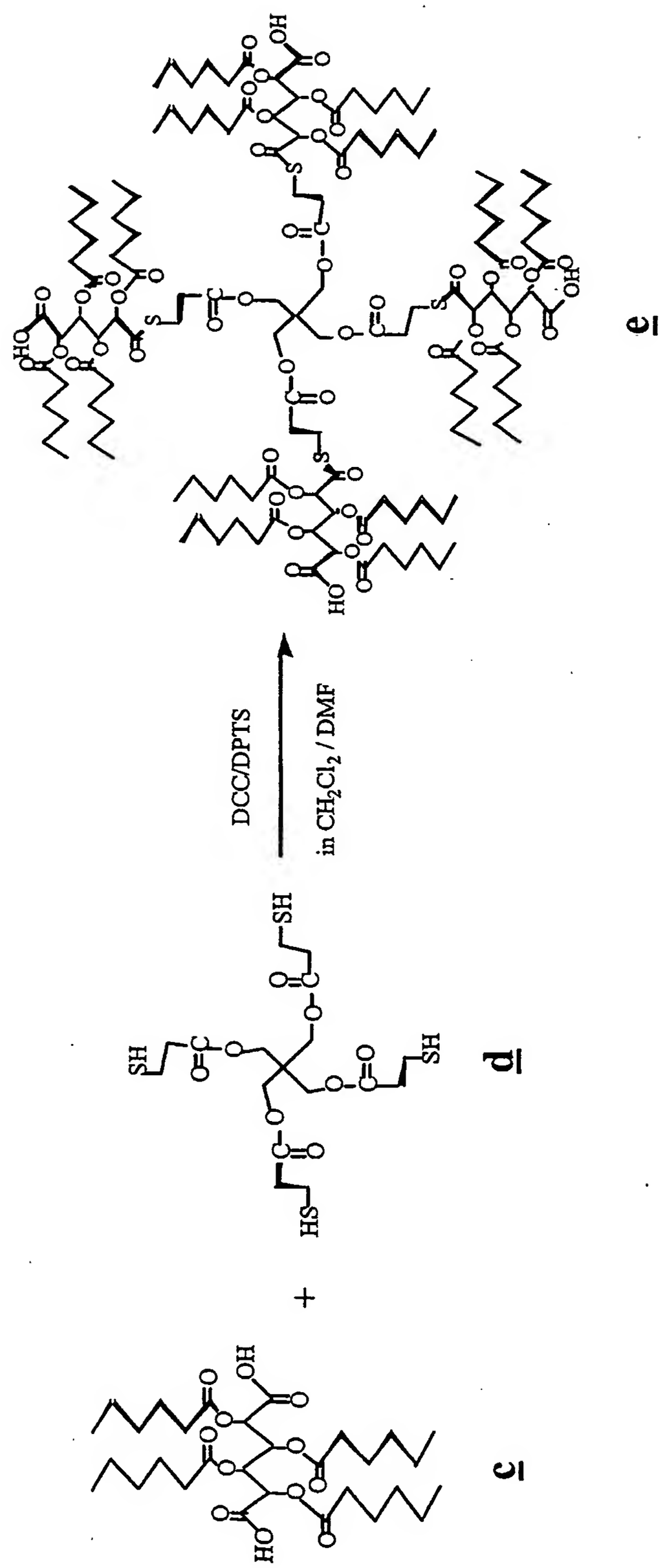
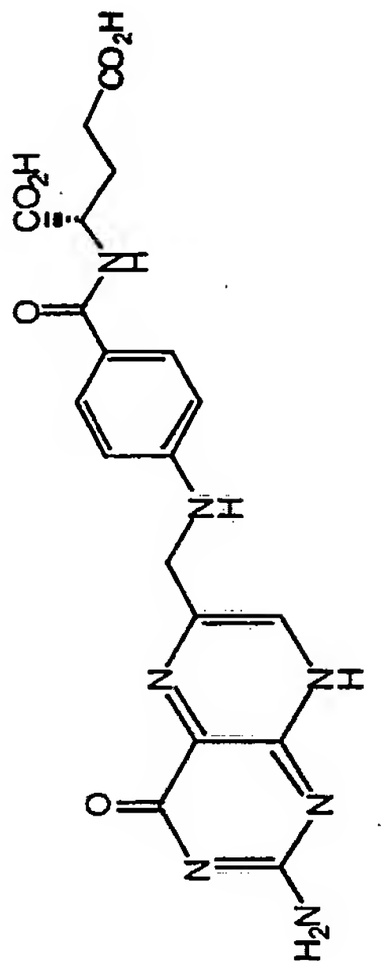
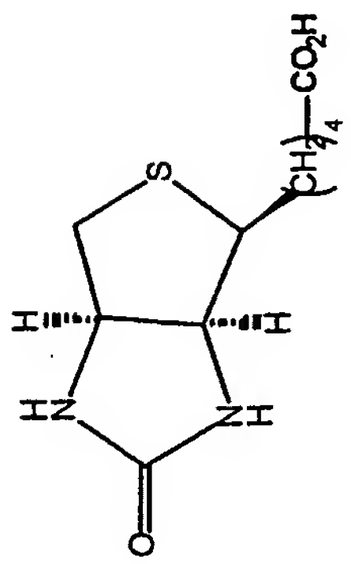


Fig. 4

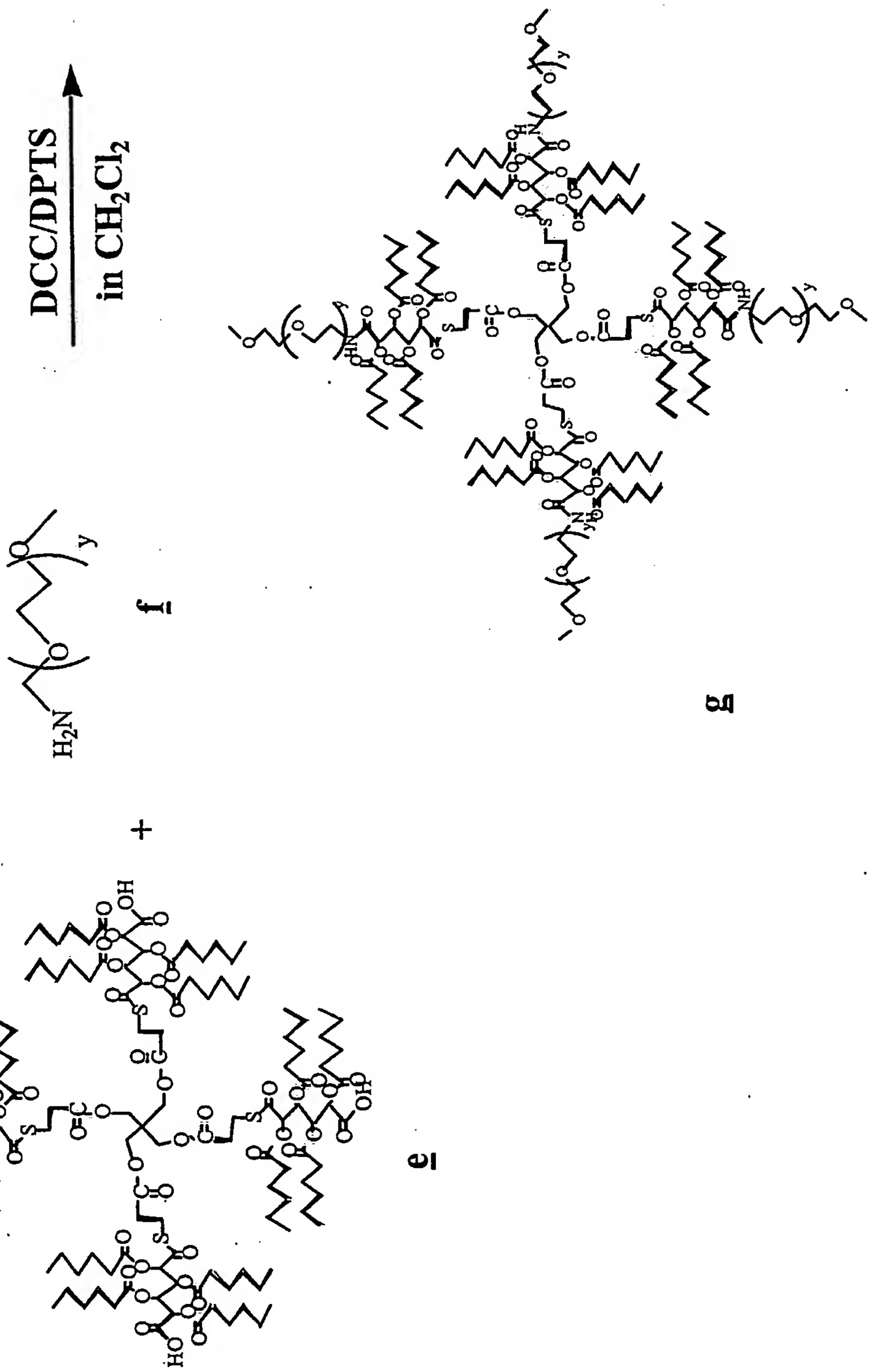
Fig 5



Folic Acid



Biotin



1a 1b 1c

Fig. 6

Fig 7

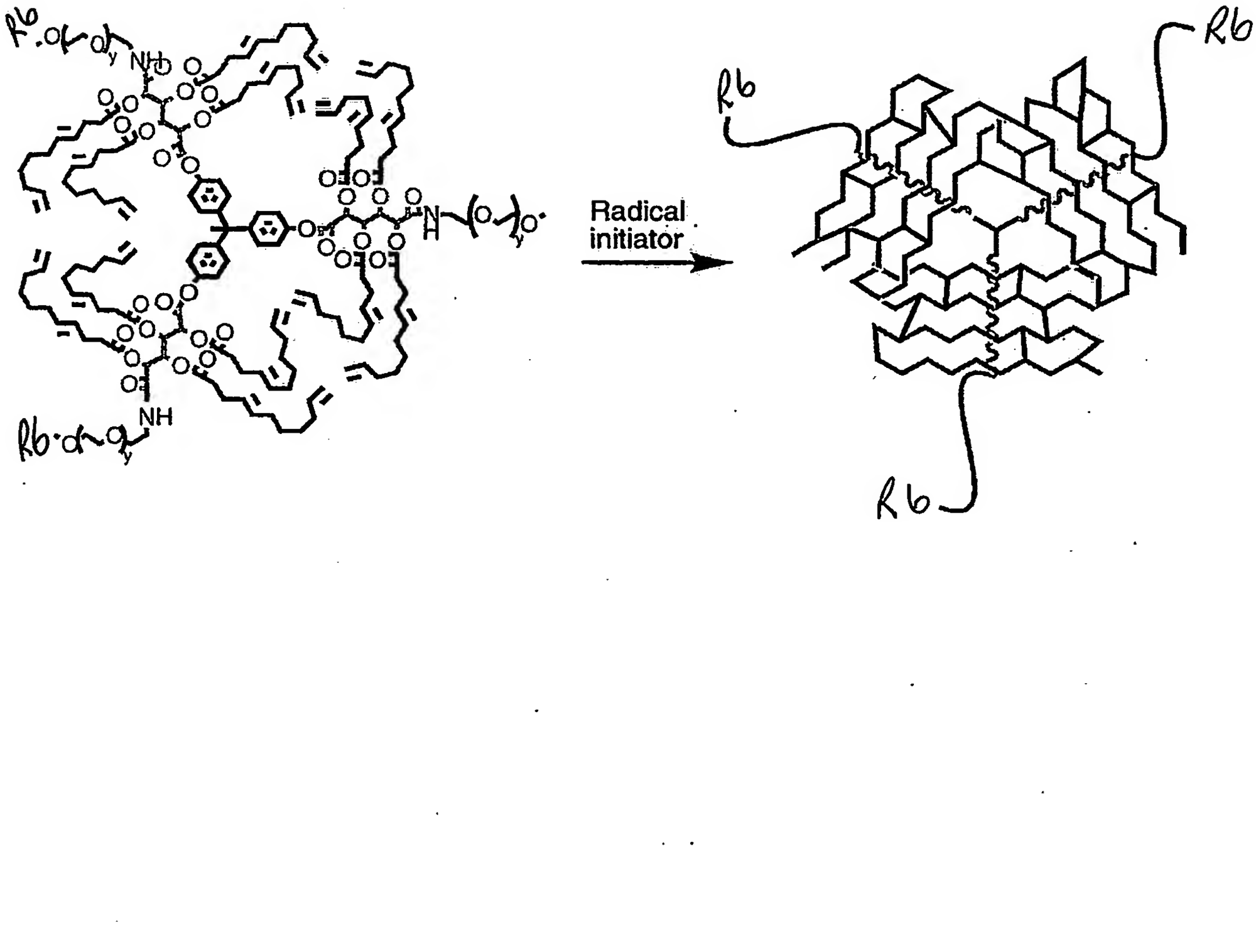


Fig 8

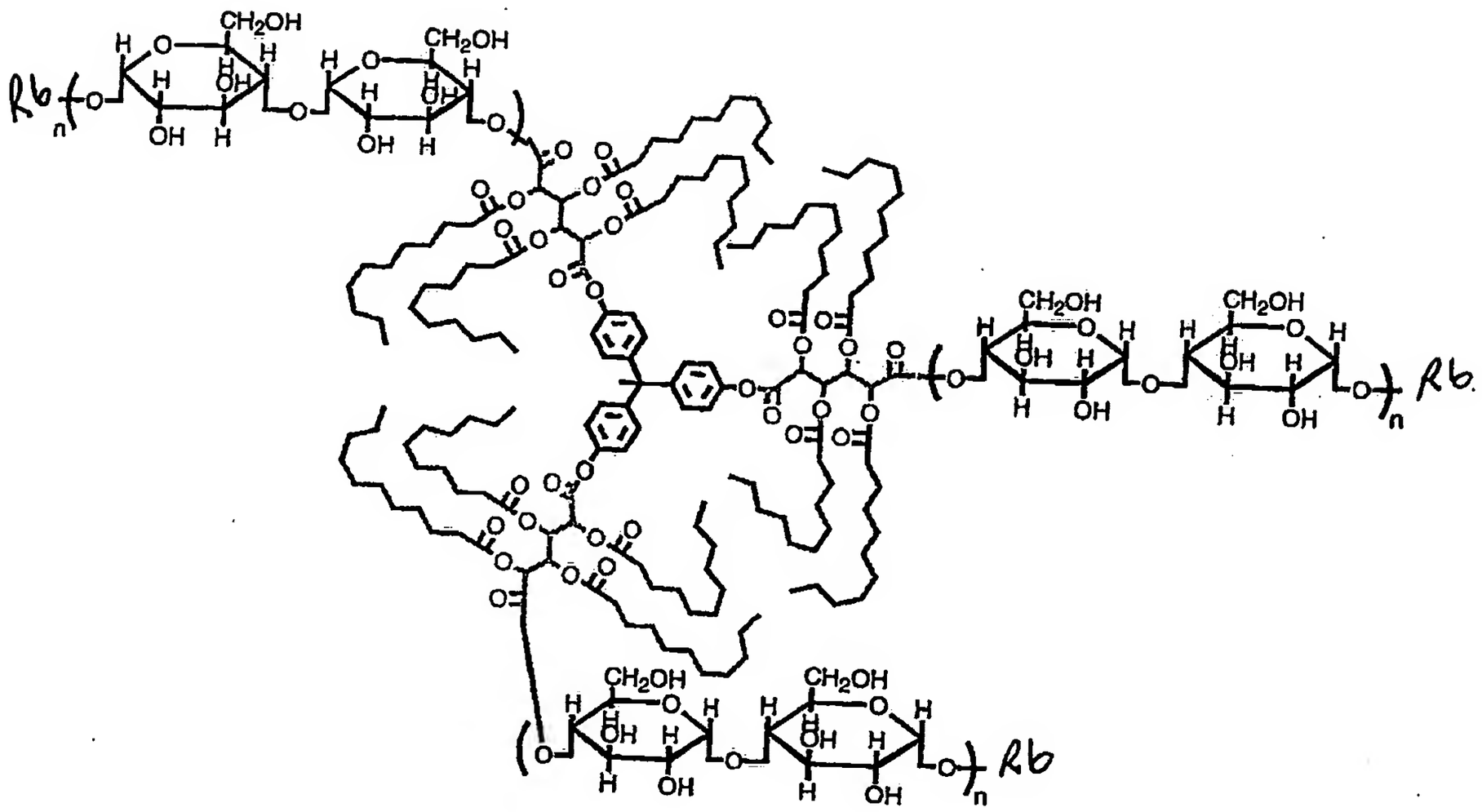


Fig 9

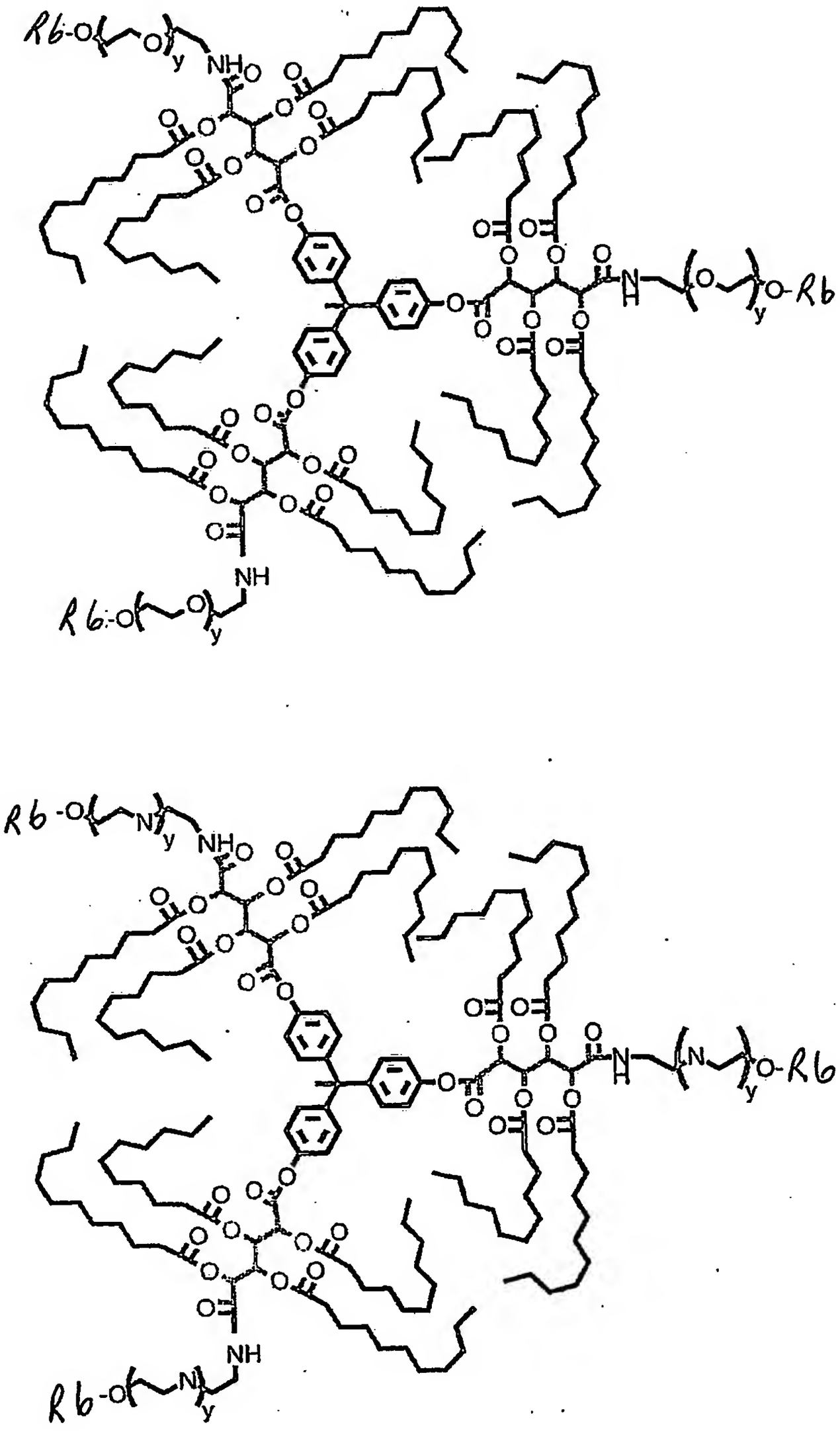


Fig 10

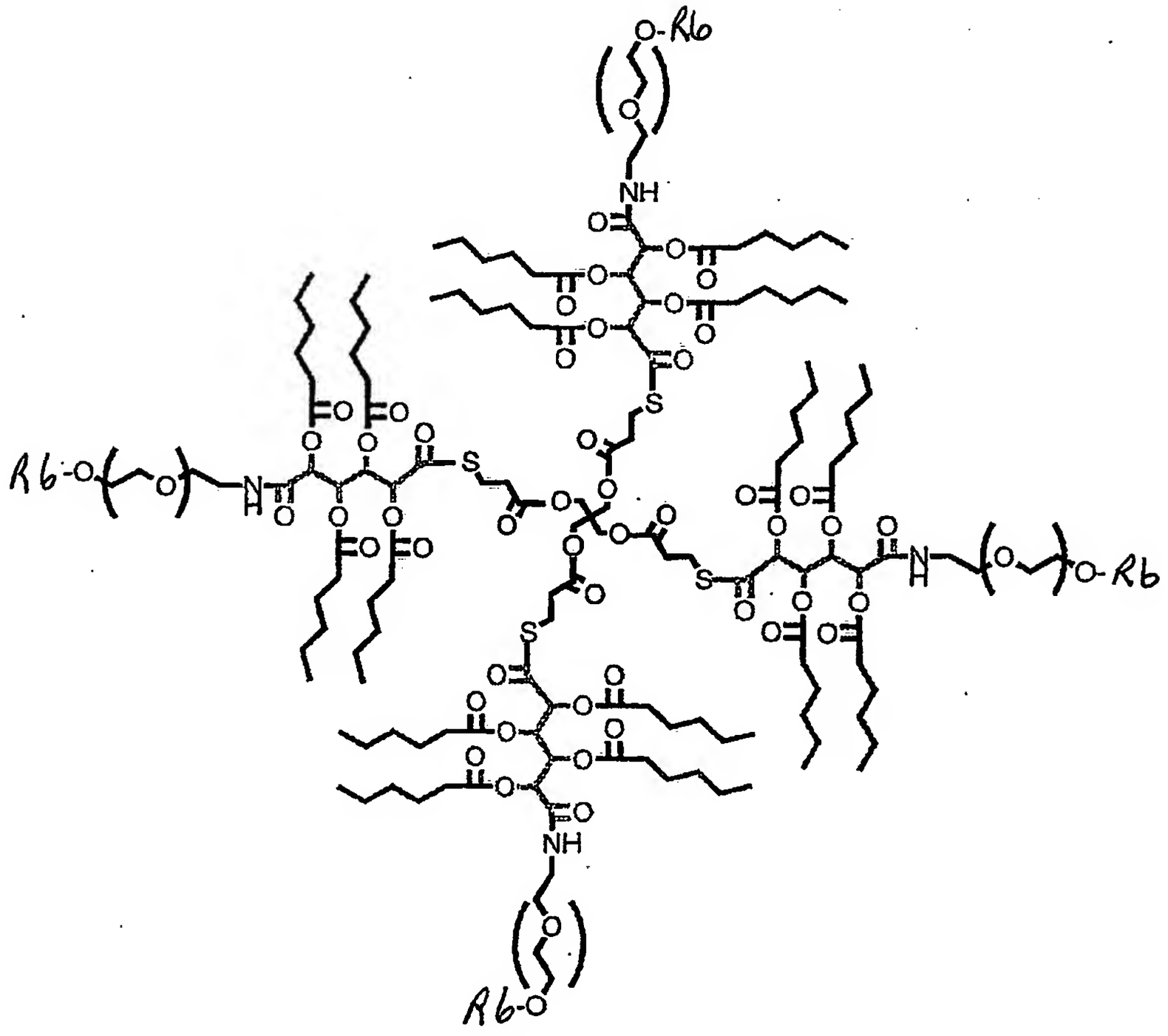
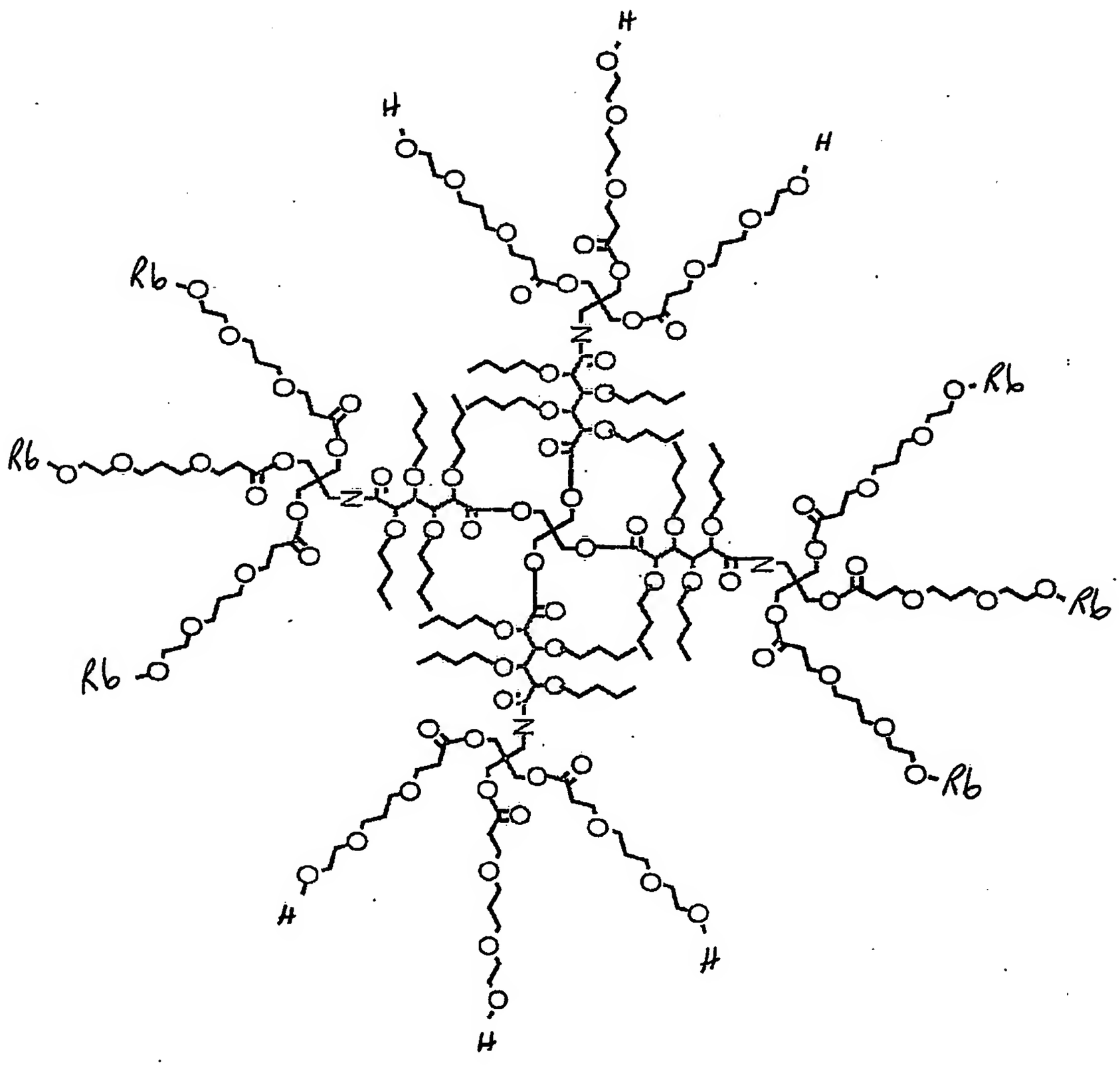


Fig 11



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Published:
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(88) Date of publication of the international search report:
9 October 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/005959 A3

(54) Title: AMPHIPHILIC STAR-LIKE MACROMOLECULES FOR DRUG DELIVERY

(57) Abstract: The present invention provides polymeric compounds that can form micelles in solutions. These compounds have a hydrophobic, core that is coupled to a plurality of hydrophilic moieties.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/21923

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07C 229/00, 69/66
US CL : 560/171, 180, 182
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 560/171, 180, 182

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JIANG et al ACS Symposium Series 1998, 709 (Tailored Polymeric Materials for Controlled Delivery Systems), pages 117-124, Page 119, Scheme I, compounds 4a-d and	1-3,44
Y,P	US 6,284,233 B1(SIMON et al) 04 September 2001(04.10.2001), column 6, lines 23-66, column 7, lines 13-47.	1-3, 44

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2003 (24.06.2003)	23 JUL 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Paul A. Zucker Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/21923

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 4
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 4 could not be search because the variable group R14 was not defined.

3. ☒ Claim Nos.: 6-43 and 45-54
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

PCT/US02/21923

INTERNATIONAL SEARCH REPORT

Continuation of B. FIELDS SEARCHED Item 3:
CAS ONLINE
search terms: mucic acid, tartaric acid, core, dendrim?, star, pentaerythritol, dicarboxylic, polymer